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THROMBOANGIITIS OBLITERANS*

An Evaluation of Therapy, with Special Reference to Lumbar Sympathectomy

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BOSTON

THROMBOANGIITIS obliterans is an uncommon disease. The diagnosis was made at the Massachusetts General Hospital in only 180 cases during the twenty-year period 1926–1945. It makes up for its infrequency, however, by its chronicity, the 180 patients having had a total of 780 different admissions, or an average of over 4 admissions per patient, each one of which averaged thirty-two days or a grand total of 24,960 patient days or sixty-eight-and-one-third patient years. Thus, the problem of therapy is of considerable importance both to the patient and on general economic grounds.

The diagnosis of thromboangiitis obliterans at the Massachusetts General Hospital is made for the most part on clinical evaluation. Surgical specimens have shown to a large extent the nonspecific histology of the inactive phase of the disease. At the Massachusetts General Hospital a young male with evidence of obliteration of the major arteries in the lower extremities without x-ray evidence of calcification and almost always with a relatively long history of intermittent claudication fulfills the necessary criteria for diagnosis. A history of migrating phlebitis, ulceration of toes, increased susceptibility to cold and excessive use of tobacco serve as confirmatory evidence.

The sufferer from thromboangiitis obliterans is relatively young, well under the age when arteriosclerosis may produce much the same clinical picture. Eighty-seven per cent of our patients were in the third to fifth decades, and 41 per cent were between thirty and forty years of age (Table 1).

It should be noted that 22 patients are listed in Table 1 as having thromboangiitis obliterans although their first admission to this hospital occurred at fifty years of age or older. We believe that by the time the age of fifty is reached thromboangiitis obliterans will seldom initiate symptoms and also that in an old case symptoms at the age of fifty may be attributed to superimposed arteriosclerosis, and yet in this group, the evidence on review of the records favors the diagnosis of thromboangiitis obliterans, although, as emphasized above, it is by no means conclusive.

Incidentally, one of these more elderly patients was one of the 2 women in our series, aged sixty-one, and the diagnosis was established by histologic examination.

TABLE 1. *Ages, by Decades, of Patients at Time of First Admission.*

AGE yr.	NO. OF PATIENTS	PERCENTAGE
10–19	1	less than 1
20–29	26	14 } 87
30–39	73	41 }
40–49	58	32 }
50–59	18	10
60–69	4	2
Total	180	

It has been mentioned above that the symptoms of intermittent claudication in thromboangiitis obliterans are usually of long duration. In this series the average interval between onset of symptoms and admission to the hospital was fifty months.

From a geographic standpoint 57 per cent of our patients were born in this country, 34 per cent in Russia or Poland, 6 per cent in Canada and 4 per cent each in Italy and Portugal. It is of interest that only 21 per cent were of Jewish extraction.

No particular occupation was engaged in by the group, there being an even spread among nine listed types of work. This is in agreement with the findings of others.[1]

Since smoking is considered a contributory cause of the failure of therapy and, by some, of the disease

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itself, we have endeavored to determine its incidence. Of 155 of the 180 patients from whom we could obtain definite information, 108 smoked more than 20 cigarettes a day; 44 smoked less than a package, and only 3 claimed that they never smoked.

Treatment

Almost all the forms of therapy that have been advocated for thromboangiitis obliterans have been employed by the Vascular Service of the Massachusetts General Hospital at some time. These include nonspecific foreign protein, intravenous administration of hypertonic saline solution and of ether, histamine, ascorbic acid and sodium citrate solution. Some of these therapies were employed on only a very few patients, but none have impressed the Vascular Service sufficiently to ensure their continued use at the Massachusetts General Hospital.

Supportive

At the present time, the treatment of legs without open lesions consists of "foot hygiene," postural exercises[2] as modified by Allen,[3] sympathectomy[4] and an attempt at education of the patient including interdiction of tobacco.

Each patient is given a printed sheet, which contains information concerning the care of the feet and toenails and also diagrams and instructions including specific timing for postural exercises. The timing is determined by observation of the period necessary to produce blanching of the feet on elevation and full engorgement on dependency. It is believed that these times should be redetermined at intervals of a month or so.

Properly performed exercises are regarded as advantageous to the patient in two ways: there is good reason to believe, on the basis of repeated observations, that the development of collateral circulation is aided, and there is a benefit to morale, because the patient realizes that he is actively engaged in the therapy of his own disease.

It has been found that the patient's interpretation of the exercises must be checked at every opportunity; otherwise, gross errors and probably no benefits result.

Many of the forms of therapy described above could be included under "general education," but a specific effort is made to inform the patient of the nature of his disease, what the prognosis is, how it may be bettered, what sort of occupation he may engage in, how pain and discomfort may be handled and, most important of all, the need for avoidance of tobacco.

Obviously, the individual patient should be viewed with a proper perspective. It is better to enjoy life without legs than to spend every waking hour doing exercises to save legs that can never be of further use. Possibly, it is better in rare cases for a patient to smoke and thereby endanger his legs than to suffer severe withdrawal symptoms, but if the patient disregards his instructions it should be because he has calculated the risk rather than through ignorance.

Sympathectomy

Lumbar sympathectomy has been considered to be the most effective form of therapy that we have employed. Since 1936 virtually all patients with thromboangiitis obliterans have had bilateral lumbar sympathectomies. This involves 85 patients.

Since the etiology is unknown and the nature of the pathologic process is not entirely clear, it is impossible to think of sympathectomy as a specific therapy. Indeed it is almost certain that remissions and exacerbation of the disease still continue unaltered, but that the symptoms are usually ameliorated. The release of vasoconstrictor impulses can affect only the undiseased collateral circulation. It is apparent, therefore, that the earlier in the course of the disease sympathectomy is performed, the more benefit should be derived. Whether sympathectomized and hitherto undiseased arteries and arterioles are protected to any extent from the encroachment of thromboangiitis obliterans is a question that at the moment cannot be answered.

Results. A follow-up study has been made in the hope of shedding light on two important questions — namely, the influence of sympathectomy on preservation of the extremity and its effect on the relief of symptoms.

Of the 170 legs that have been sympathectomized, 23, or 13.5 per cent, were subsequently amputated. If cases in which amputation was performed less than three months after sympathectomy are excluded (and since in many of these cases sympathectomy was performed as a last resort it seems reasonable to exclude them), the amputation rate is lowered to 9.4 per cent. These figures are to be compared with the 67 (35.2 per cent) of the total 190 legs not subjected to sympathectomy that were amputated. The figures are not, of course, strictly comparable since the unsympathectomized groups to a large extent were treated early in the twenty-year period, before some of the more modern concepts of general therapy were evolved, and also because there has been a longer period in which further arterial obliteration might develop. Nevertheless, it appears probable that some legs have been preserved by sympathectomy.

In an attempt to evaluate the symptomatic relief following lumbar sympathectomy, it was obvious that evaluation, difficult enough in any case, had better be confined to a definite symptom such as pain. We turned our attention, therefore, to patients with intermittent claudication or steady pain in their extremities unassociated with an open ulcer at the time sympathectomy was done. This strict requirement gave us only a small group of 30 extremities belonging to 18 patients that we

carefully studied. The patients were personally interviewed and examined.

The results are summarized in Table 2, which shows that although only 60 per cent of the extremities that could be evaluated showed improvement in intermittent claudication, 86.6 per cent demonstrated improvement in general comfort — that is, increased warmth, disappearance of numbness and so forth.

TABLE 2. *Results One Year or More after Lumbar Sympathectomy in 24 Patients.*

RESULT	GENERAL DISCOMFORT NO. OF CASES		INTERMITTENT CLAUDICATION NO. OF CASES	
Patient cured	2		3	
Patient greatly improved	18	(86.6%)	4	(60%)
Patient improved	6		8	
Patient unimproved	2		6	
Patient worse	2		4	
Total limbs evaluated	30		25	

Some[5] have believed that sympathectomy should be more efficacious in patients with less damage to the circulation as evidenced by palpable popliteal pulsations. Table 3 shows that we have not found this to be true. The good and poor results are about evenly distributed among the patients with and without palpable popliteal pulses.

The optimum extent of lumbar sympathectomy has always been debated. The debate has centered around whether the first lumbar ganglion should be removed along with the second and third or whether removal of the latter two alone is sufficient. Although evaluation of this point can never be finally made until postoperative testing of the sympathetic denervation is accurately done, we have some information derived from the operator's impression of the extent of the sympathectomy performed. Table 4 correlates the removal or nonremoval of the first lumbar ganglion with the effect on intermittent claudication. Although the numbers are too small to be conclusive, there is no tendency for them to suggest that the additional removal of the first lumbar ganglion contributed markedly to the subjective result.

TABLE 3. *Correlation of Presence or Absence of Popliteal Pulse with Improvement in Intermittent Claudication (25 Extremities).*

STATUS OF INTERMITTENT CLAUDICATION	STATUS OF POPLITEAL PULSE AT TIME OF SYMPATHECTOMY	
	PRESENT	ABSENT
Cured		3
Greatly improved	3	1
Improved	4	4
Unimproved	2	4
Worse	2	2
Totals	11	14

The danger of interfering with sexual function is always debated when the extent of lumbar sympathectomy is considered for patients in this age group. We were able to analyze the results on 16 patients who had had unilateral (5) or bilateral (11) lumbar sympathectomy. We found that none of the 5 patients who had had a unilateral lumbar sympathectomy of any degree (4 of our 5 included the first lumbar ganglion) had any trouble with potency or ejaculation. Of the bilateral lumbar sympathectomies the first lumbar ganglion was removed bilaterally in 6 patients, all of whom had some trouble with sexual function (3 with ejaculation, and 3 with potency). In 1 of these patients the trouble with ejaculation was only temporary, lasting for three months. In another, ejaculation was not abolished but decreased by 75 per cent. In the other 4 cases trouble was complete and permanent. Two of the patients with bilateral lumbar sympathectomies had the first lumbar ganglion removed on one side but not on the other. Both had complete and permanent loss of ejaculatory power. In 2 patients only of the bilateral group were the first lumbar ganglions spared on both sides. Neither of these showed any interference with sexual function. Poppen and Lemmon[6] found that 39 per cent of males who had the first and second lumbar ganglion removed from above on both sides for arterial hypertension had trouble with sexual function. They postulated that lower lumbar ganglions often participate in the regulation of such function. From this point of view, therefore, as well as from that of the clinical result, it is concluded that it is rarely advisable or necessary to remove the first lumbar ganglion when a lumbar sympathectomy for thromboangiitis obliterans is performed in young men. It is also important, if a bilateral operation is to be performed, to warn the patient of possible trouble, since owing to the variable arrangement of ganglions in this region,[7] it is not always possible to preserve the first lumbar ganglion.

TABLE 4. *Correlation of Removal or Nonremoval of the First Lumbar Ganglion with Effect in Intermittent Claudication (25 Extremities).*

EFFECT ON INTERMITTENT CLAUDICATION	FIRST LUMBAR GANGLION REMOVED NO. OF CASES	FIRST LUMBAR GANGLION NOT REMOVED NO. OF CASES
Cured	—	3
Greatly improved	1	3
Improved	7	1
Unimproved	4	2
Worse	2	—
Totals	14	9

Since only 5 of the 18 patients could be said to have definitely abstained since the diagnosis was first made, the effect of smoking on this group of

patients could not be accurately assessed. Of the 7 extremities in these 5 patients, 6 were improved in varying degrees; only 1 was unimproved. We are of the opinion, from talking to the patients who did not abstain, that there is a great individual variation in sensitivity to smoking in patients with thromboangiitis obliterans. Separation of the sensitive from the nonsensitive persons can be made, however, only by a process of trial and error that, at best, is unsatisfactory. Furthermore, it is well known that even those who are most sensitive will often continue to smoke in the face of the threatened loss of a limb. We therefore consider that a strict edict should be issued to all patients with thromboangiitis obliterans that they abstain from smoking for life.

It is important that the surgeon have some knowledge of when maximal improvement may be expected to follow sympathectomy. In 13 of the 16 patients who were improved after lumbar sympathectomy, the maximal improvement was immediately established in 6. In 3 the improvement was complete within two months. By the end of a year the remaining 4 had experienced all the improvement that they obtained.

Amputation

Ninety legs were amputated in 64 patients (26 patients had bilateral amputations). This is an incidence of 25 per cent legs lost. Many of these operations were performed soon after the patient was first seen at the hospital and so do not represent a failure of therapy; however, the incidence is high.

Of the amputations done above the level of the metatarsals, 18 were done at the point of election in the lower leg. Twenty-seven were low-thigh and the remainder or 45 were Gritti–Stokes amputations. Because of the relative youth in this group and the fact that in thromboangiitis obliterans arterial obliteration tends to be more peripheral and the collateral circulation better than in arteriosclerotic gangrene, the Gritti–Stokes amputation is usually to be preferred over the more conservative low-thigh amputation. It gives a weight-bearing stump that is relatively easy to fit with a prosthesis and allow maximum activity.

However, it is probable that with modern therapies such as sympathectomy and chemotherapy more lower-leg amputations should be performed than we have thought permissible in the past.

Minor amputations. Minimal gangrene is frequently best treated by amputation of one or more toes. In our series 47 patients, or 26 per cent, had amputations that averaged three and three-tenths toes apiece.

Toe amputations should never be done until the level of gangrene has been clearly established and it appears probable that the resulting wound will heal. Crushing of the appropriate peripheral nerves as described by Smithwick[8] continues to prove a useful form of therapy. It is of great value in certain patients with painful open lesions when the sensory denervation may allow adequate daily dressings and the sympathetic denervation some additional beneficial release of vasoconstrictor impulses. At present, transmetatarsal amputation, as recommended by McKittrick[9] in diabetic patients, is considered as an alternative to multiple toe amputations. We have performed a few highly successful ones in patients seen since this series was concluded.

Although thromboangiitis obliterans may be a generalized arterial disease, only 10 of our patients, or 6 per cent, have required amputation of fingers. No amputation above the level of the finger was required in the upper extremity. In these 10 patients a total of 40 fingers were amputated. In two patients who had lost almost all their digits as well as both legs, the finger stumps still showed nicotine stains indicating that smoking is indeed most difficult to give up.

Seventeen upper extremities were sympathectomized. It is impossible to draw conclusions about the result of these operations except that the subjective impression was favorable.

Discussion

In reviewing this series of patients with thromboangiitis obliterans, we are impressed by the severity and chronicity of the disease. That our therapy has improved is manifest by the decrease in length of hospital stay. The group as a whole required thirty-two days for each admission. In 1945 the average admission had become reduced to nineteen days. The patient today is far more likely to be economically self-supporting than he was a decade ago. This we attribute mostly to comfort or lack of pain brought about by sympathectomy.

That more must be accomplished therepeutically is obvious, but it appears unlikely that great strides will be made until a better understanding of the nature and cause of the disease is arrived at.

Summary

Experiences at the Massachusetts General Hospital in the treatment of 180 patients with thromboangiitis obliterans in the twenty-year period 1926-1945 are described.

The natural course of the disease is reviewed, and useful therapeutic measures are outlined.

Although 35 per cent of 180 patients required one or more major amputations, lumbar sympathectomy early in the course of the disease has materially reduced the incidence of major amputations and has proved to be the most valuable method of therapy in our experience.

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PARENTERAL AND AEROSOL ADMINISTRATION OF ANTIHISTAMINIC AGENTS IN THE TREATMENT OF SEVERE BRONCHIAL ASTHMA*

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IT IS a widely held opinion that bronchial asthma may be due to the liberation of free histamine from its usually bound state,[1-4] although many conflicting observations make this view far from universal. The oral administration of "antihistaminic" drugs (blocking agents) has proved of limited value in the management of bronchial asthma.[5-7] Recent observations by other investigators and the results of protection studies performed in our laboratory have suggested that the parenteral use of these drugs may be indicated in the treatment of severe bronchial asthma.

Feldberg[8] and Szczygielski[9] have shown that histamine is capable of causing the release of epinephrine from the adrenal medulla. Staub[10] and Farrerons-Co[11] have demonstrated essentially the reverse of this phenomenon — namely, that the intravenous injection of epinephrine or sympathin produces a marked increase in plasma histamine. This reciprocal relation has been termed the "histamine-sympathin see-saw." The epinephrine-fast state in intractable asthma may be a disruption of this "see-saw."[12-14] In this condition large amounts of histamine are possibly present owing to allergic "shock,"[15] anoxia[16] and the further outpouring of histamine consequent upon continued epinephrine release from the patient's own adrenal medulla, and the repeated therapeutic administration of epinephrine. The "epinephrine-fast" patient may therefore present a situation similar to histamine being essentially unopposed. It is in this connection that the administration of specific antihistaminic agents would exhibit whatever value they may have in the clinical management of asthma, by "balancing" the deranged histamine-sympathin "see-saw."

Yonkman and his associates[17-19] described potentiation of the effects of epinephrine in the cat after the administration of tripelennamine. This "adrenergic potentiation" was observed in both excitatory and inhibitory effector mechanisms. Similar potentiation of the vascular effects of epinephrine, after Antergan,[20] Benadryl[21, 22] and Neoantergan,[23, 24] as well as tripelennamine, has been reported by other observers. Experiments are in progress to determine whether antihistaminic agents have the ability to potentiate the protection afforded by sympathomimetic drugs, anticholinergic drugs and aminophylline against histamine-induced and methacholine-induced dyspnea and bronchospasm in patients with bronchial asthma.[25]

Oral administration of antihistaminic agents may prove undependable. It has been shown that occasional patients, who demonstrated poor protection against histamine-induced dyspnea and bronchospasm when these drugs were administered orally, did show significant protection when the intravenous, rectal and aerosol routes were employed.[26] Taub[27] obtained clinical relief from various allergic phenomena following parenteral administration of antihistaminic agents after large oral doses of these drugs had proved ineffective. Rosenberg and Blumenthal[28] reported 4 cases of poison-ivy dermatitis in which immediate relief of pruritus followed intravenous injection of diphenhydramine. One subject was then placed on a maintenance dose of 50 mg. orally every four hours and then 100 mg. every two hours and experienced no relief. The authors concluded that "the only explanation felt plausible is that absorption from the gastrointestinal tract was impaired." Serafini,[29] McGavack[30] and Arbesman[31] have also noted variable absorption rates of antihistaminic drugs from the gastrointestinal tract during the course of various studies.

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Comparative Protection Studies Employing Diphenhydramine and Tripelennamine by Various Routes

An analysis of Figure 1 and 2, in which are summarized the degree of protection afforded by oral, intravenous, rectal and aerosol administration of diphenhydramine and tripelennamine against histamine-induced and methacholine-induced dyspnea and bronchospasm in asthmatic subjects reveals the following significant features, which suggested the possible value of these agents in the management of the asthmatic patient.

Significant protection (40 per cent) is not attained until sixty and ninety minutes with oral diphenhydramine and tripelennamine, respectively. Immediate and almost complete antihistaminic protection is conferred by the intravenous and aerosol routes. High degrees of antihistaminic activity are reached within fifteen to thirty minutes by the rectal route. Somewhat greater protection against methacholine-induced dyspnea and bronchospasm is obtained by these agents administered by the intravenous and rectal routes. The intensity and duration of significant antihistaminic protection conferred by the aerosol route (about two hours) is remarkable considering the minute dose employed. The technics used in the assembling of these data, by which controlled conditions not usually present at the bedside can be achieved, have already been fully described.[32, 33]

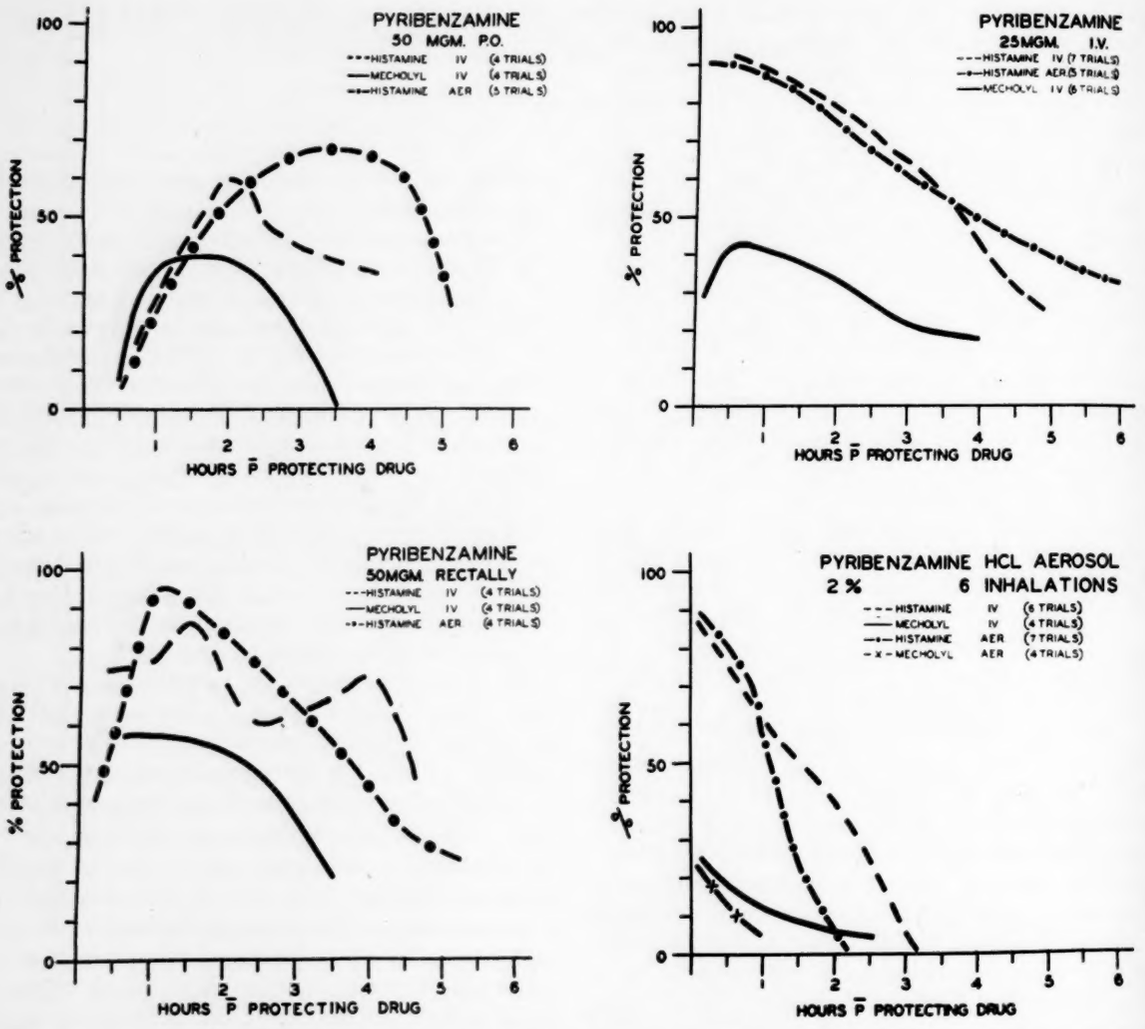

Figure 1. *Protection Afforded by Oral, Intravenous, Rectal and Aerosol Administration of Tripelennamine Hydrochloride (Pyribenzamine) against Dyspnea and Bronchospasm Induced by Histamine and Methacholine in Asthmatic Patients.*

Methods

We have used diphenhydramine* and tripelennamine† in the treatment of 15 patients seriously ill with bronchial asthma. Doses ranged from 20

*Kindly supplied by G. D. Searle and Company, Chicago, Illinois.

†Kindly supplied by Ciba Pharmaceutical Company, Summit, New Jersey (Pyribenzamine).

to 50 mg. of either agent and were administered intravenously at a rate not exceeding 10 mg. per minute. To avoid chemical incompatibility, these drugs should not be mixed with solutions of aminophylline; if an infusion containing the latter drug is being administered, the antihistaminic agent may be injected into the rubber tubing close to the needle.

The most common side reactions observed in our patients were drowsiness and dizziness, particularly in the upright position, which usually disappeared gradually within one or two hours. Other less frequent effects noted in a total of 102 separate administrations of diphenhydramine were headache, transient chilliness, nausea, fatigue, palpitation, pallor, blurred vision, tachycardia and the "alert reaction." Essentially similar side reactions were encountered in 43 intravenous administrations of tripelennamine. In some cases a moderate diminution of expectoration and an increase in the tenacity of the sputum were noticed several hours after the administration of tripelennamine, which McElin and Horton[34] have also observed and which is possibly related to its anticholinergic properties.

Once having relieved the severe bronchospasm, we have successfully maintained many of our patients during convalescence with antihistaminic agents by the aerosol or rectal routes, or both, as supplements to other therapy. The aerosol route, employing a 2 or 5 per cent tripelennamine solution, either alone or mixed in equal parts with a bronchodilator, in a Vaponefrin nebulizer, has afforded gratifying relief. This is especially true when physical factors such as exposure to cold appear to play an important role. Rectal administration of tripelennamine or diphenhydramine (25 to 50 mg.) has likewise been surprisingly efficacious over prolonged periods. For rectal instillation one may employ capsules of diphenhydramine, puncturing

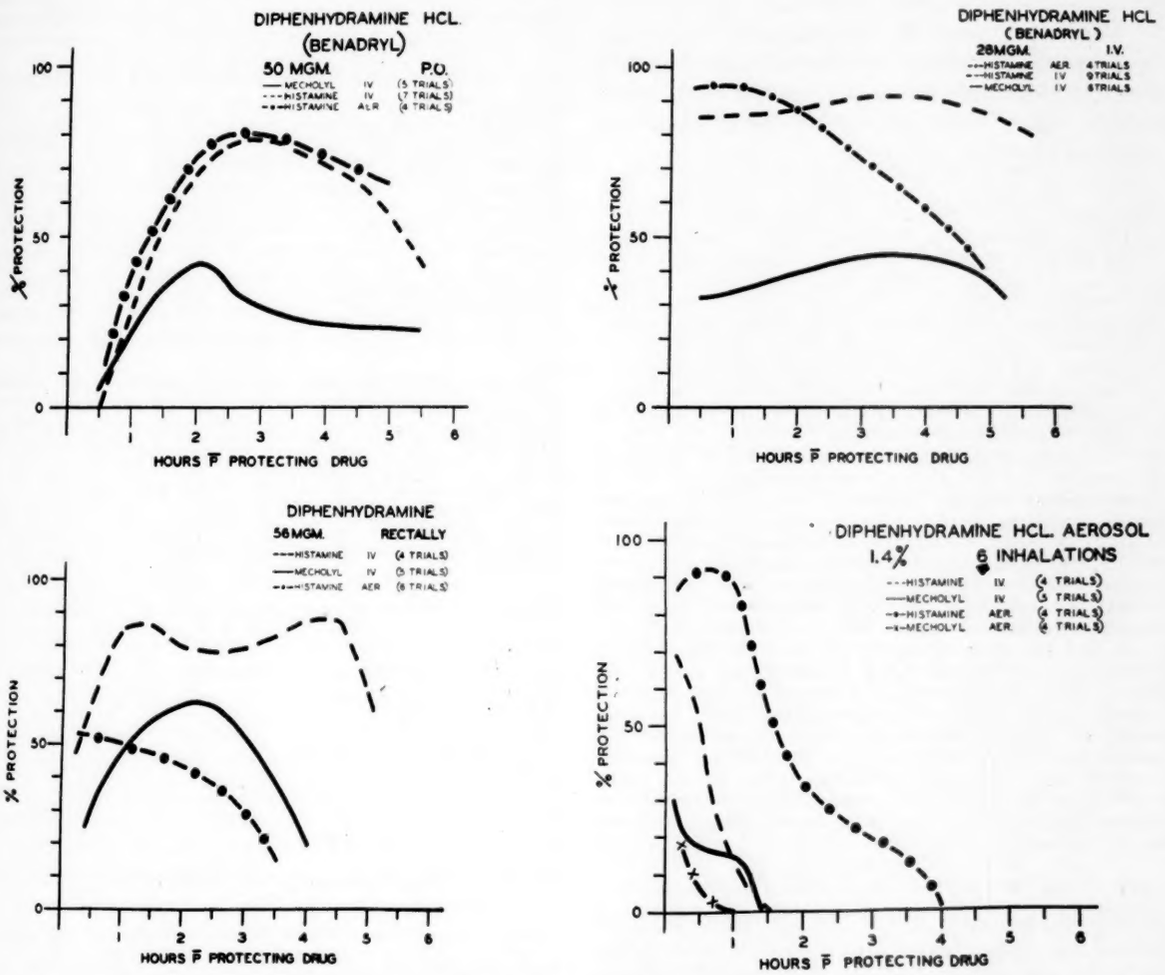

FIGURE 2. *Protection Afforded by Oral, Intravenous, Rectal and Aerosol Administration of Diphenhydramine against Dyspnea and Bronchospasm Induced by Histamine and Methacholine in Asthmatic Patients.*

the ends of the capsule before insertion into the rectum, or either drug may be given in solution, alone or in combination with aminophylline. Addition of diphenhydramine to solutions of aminophylline may result in the formation of a milky suspension; this reaction apparently does not interfere with the action of either drug given rectally.

The 15 patients in this series were selected after they had proved partially or completely refractory to either one or a combination of the following: epinephrine subcutaneously, various bronchodilator aerosols, aminophylline intravenously or rectally, meperidine, helium-oxygen and "bronchial catharsis." Whenever possible, vital-capacity readings were taken in an attempt to obtain more objective evidence of improvement in pulmonary ventilation. Significant relief or restoration of epinephrine sensitivity was afforded in 10 cases.

Case Reports

Case 1. E. S. a 26-year-old woman, had had eczema and perennial bronchial asthma all her life, necessitating eight previous hospitalizations. There was a history of familial allergy. She had had pneumonia at the age of 16. Decreases in her vital capacity of 1000 cc. or more could regularly be induced during asthma-free periods by the intravenous injection of 0.01 to 0.02 mg. of histamine. She had been maintained comfortably on bronchodilator aerosols for many months; many oral preparations and rectal administration of aminophylline had afforded no relief.

After an absence of 3 months, she returned to the clinic on September 10, 1948, with a history of increasingly severe bronchial asthma over the previous 4 days. She was greatly fatigued, somewhat tremulous and so dyspneic that it was impossible to obtain satisfactory vital-capacity determinations. She had been taking epinephrine subcutaneously every hour or so and bronchodilator aerosols even more frequently, with rapidly diminishing relief. Intravenous and rectal administration of aminophylline was likewise essentially ineffective and merely precipitated an "alert reaction." After six inhalations of Isuprel (1:200 solution) had proved ineffective, 25 mg. of tripelennamine was given intravenously. The dyspnea was greatly relieved after only 5 mg. had been injected. By the time the total amount was given, she was no longer dyspneic; her vital capacity was 1800 cc. The only side effect noted was mild drowsiness. Ten minutes later, six inhalations of Isuprel 1:200 were again administered with an immediate rise of her vital capacity to 2200 cc., at which level it remained.

In the light of this patient's previous history, it is probable that were it not for the dramatic relief afforded by the intravenous injection of tripelennamine, hospitalization would have been necessary. Although not so impressive as in the other cases reported, the restoration of sympathomimetic sensitivity resulting from the antihistaminic is nonetheless noteworthy.

Case 2. M. G., a 22-year-old single woman had had bronchial asthma for 11 years, at first seasonal but later perennial. Prior to being followed in our clinic, frequent hospital admissions had been necessary. She exhibited sensitivity to dust, mixed feathers and several foods, both clinically and by skin tests. When she was symptom free, predictable drops in her vital capacity of 1000 cc. or more could be produced with 0.015 mg. of histamine intravenously.

The effectiveness of intravenous antihistaminic therapy has been dramatically demonstrated in this patient on many occasions. On August 31, 1948, at the height of the ragweed-pollen season and during the course of a protection study in which histamine was being employed intravenously as the bronchospastic agent, she experienced moderate asthma, lasting more than an hour. Her highest vital capacity was 2400 cc., whereas her usual control readings ranged from 3600 to 4000 cc. Isuprel inhalations were without effect. Tripelennamine hydrochloride, 25 mg., was then administered by vein. Her vital capacity rose to the normal level (3500 cc.) in 3 minutes, but dyspnea and falling vital capacity recurred, and the effects of tripelennamine were no longer discernible 30 minutes later. Isuprel (1:200 solution, six inhalations) was given again at this time, with an increase in vital capacity to 4200 cc. and relief lasting 80 minutes. Her asthma then recurred once more, and Isuprel (1:200 aerosol solution, nine inhalations) was ineffective. She was given 28 mg. of diphenhydramine intravenously, diluted to 5 cc., with almost instantaneous relief after 1 cc. had entered the vein. A vital capacity of 3400 cc. was maintained for 30 minutes, and, as it began to drop, Isuprel (six inhalations) produced a further rise to 4000 cc. She remained at this level for 1 3/4 hours, and was discharged for the day, essentially asymptomatic. No side reactions from either drug were noted.

On September 9 the patient returned with severe bronchial asthma, which had been refractory to Isuprel aerosol, rectal administration of aminophylline, and epinephrine injected subcutaneously. She was perspiring profusely and extremely dyspneic, and was unable to blow up the vital-capacity apparatus. Diphenhydramine, 28 mg., was slowly administered intravenously. No sooner had the injection been begun than a profound relief again occurred and was objectively manifested by vital-capacity readings of 2000 cc. within 5 minutes. Ten minutes after the diphenhydramine, Isuprel (1:200 solution, six inhalations) was given with even further relief. Her vital capacity rose to 3200 cc., at which level it persisted for 90 minutes. As before, no drowsiness or other effects were noted.

On November 12, after sudden changes in the weather, which had frequently precipitated asthmatic paroxysms in the past, she came to the clinic in severe bronchospasm that again was refractory to her usual therapy. She was given ten inhalations of an aerosol produced from a 1.4 per cent solution of diphenhydramine. Her vital capacity, which had been unobtainable, rose to 2800 cc., and after six inhalations of Isuprel 1:200 aerosol, it increased to 3200 cc., at which level it persisted for over 1 hour.

There is little doubt that parenteral antihistaminic therapy prevented not only hospitalization but also the progression of the asthma to the truly intractable state. Restoration of sensitivity to bronchodilator drugs with "adrenergic potentiation" was clearly and objectively demonstrated on the three occasions here reported and during several exacerbations since. It seems that diphenhydramine is the preferable drug in the patient, although no notable side effects occurred with either agent.

Case 3.* M. K., a 55-year-old married woman, had suffered from bronchial asthma for 4 years. Until her present illness, the attacks had never been severe and had generally been relieved by epinephrine subcutaneously. Repeated skin tests were reported as negative. It was believed that emotional factors, as well as respiratory infections, contributed greatly to recurrences of the asthma. In April, 1948, a severe attack of asthma, which necessitated hospitalization, developed. On an extensive program of continuous aminophylline infusions in 5 per cent glucose and water, meperidine and aerosols of a bronchodilator spray, she made a good recovery and was discharged within 10 days.

She then remained essentially well for 2 weeks, when she had a relapse and once again presented a picture of typical status asthmaticus. At this time she was entirely refractory to a continuous intravenous infusion of aminophylline, sympathomimetic amines by various routes, oxygen and numerous sedatives. She was then started on a program of intravenous injections of tripelennamine, 50 mg. every 4 hours. After the initial dose, bronchospasm became less marked, and the patient was considerably relaxed and somewhat drowsy. These injections were continued for the first 24 hours, and

*This case has previously been reported elsewhere.[14]

the dose was gradually lowered to 40, 30, and 20 mg. at intervals of approximately 1 day. The drug was entirely discontinued after 5 days of treatment.

Approximately 20 minutes after the initial intravenous dose of tripelennamine she was given 0.3 mg. of epinephrine subcutaneously. Subsequently, dyspnea and wheezing became still less marked. Furthermore, she did not complain of the troublesome palpitation and headache that epinephrine had produced previously. After the second injection of the antihistaminic agent, it was observed that she could once again return to aerosols of one of the sympathomimetic amines with considerable relief and without the side reactions previously observed. It was further noted that her tolerance for aminophylline returned under this program. She continued to make excellent progress, and after the 5th day all intravenous therapy was discontinued and she was placed on a program of rectal administration of aminophylline and tripelennamine and aerosols of one of the sympathomimetic amines. She has remained symptom free under this program.

These results are of particular interest because they demonstrate that restoration of epinephrine and aminophylline sensitivity can also be obtained in patients with "intrinsic" bronchial asthma with parenteral antihistaminic therapy. Several other favorable effects of this regimen that merit comment are the desirable sedative side reactions in such patients and the absence of the nausea and the "alert reaction" that aminophylline had previously produced.

Case 4. J. S., a 24-year-old single unemployed veteran' had had hay fever and asthma for the past 2 years, occurring from May to the first frost. Prior to coming to the clinic, he had required injections of epinephrine and aminophylline every evening on the Accident Ward. With Hydryllin, Isuprel aerosol and rectal administration of aminophylline, he fared very well for 3 weeks during his usually worst season.

On September 7 he entered the clinic with severe bronchospasm. His vital capacity was 1600 cc., as compared with previous readings, which varied from 4600 to 5000 cc. Neither Isuprel aerosol nor rectal administration of aminophylline had helped. Epinephrine, 0.25 mg., was given subcutaneously. Only slight clinical improvement was noted with an increase in vital capacity to 2400 cc. 5 minutes later. His asthma recurred in a short time, however, and his vital capacity fell to 1300 cc. After the intravenous injection of 28 mg. of diphenhydramine, marked relief was experienced with a rise in vital capacity to 3200 cc. Five minutes later, Isuprel (1:200 solution, six inhalations) effected a further increase of vital capacity to 3800 cc.; this state persisted for 45 minutes longer before he was sent home.

Here again, sensitivity to sympathomimetic agents following intravenous antihistaminic therapy was promptly restored. The patient experienced moderate drowsiness and drying of the pharynx and tracheobronchial tree, which subsided within two hours.

Case 5. W. S., a 17-year-old boy, had had asthma for 15 years occurring concomitantly with hay fever from June to early August. He had been hospitalized three times with severe "epinephrine-fast" and "aminophylline-fast" asthma. Predictable bronchospasm could be produced with intravenous or aerosol administration of methacholine; the patient exhibited no change in vital capacity after 0.05 mg. of histamine intravenously.

On September 6, 1948, he entered the clinic with moderately severe bronchospasm, his vital capacity being 1400 cc. (His usual readings varied from 4000 to 4900 cc.) Epinephrine, 0.25 mg. subcutaneously, produced no clinical response, and 20 minutes later his reading was only 200 cc. higher. Twenty-eight mg. of diphenhydramine was administered intravenously, with no appreciable change in vital capacity, although he did comment that his chest "felt lighter." When 0.25 mg. of epinephrine was again injected 10 minutes later, almost complete relief of the dyspnea occurred, with a rise in vital capacity to 2400 cc., which persisted for 1 hour. He was then discharged, the slight drowsiness produced by the diphenhydramine having subsided.

In view of this patient's past history of resistance to epinephrine and aminophylline preceding his three previous hospital admissions, it seems that restoration of sensitivity to epinephrine avoided hospitalization and further distress. We have noted similar results from intravenous injection of diphenhydramine, particularly in elderly patients and patients who were relatively histamine-insensitive during protection studies, relief being forthcoming not so much from the antihistaminic per se as from the sympathomimetic agent after sensitivity had been restored.

Case 6. I. C., a 24-year-old married woman, gave a history of seasonal bronchial asthma and hay fever of 6 years' duration. When first seen on the ward she was anxious, tense and moderately dyspneic after having received little or no objective relief from two injections of epinephrine and 0.5 gm. of aminophylline given intravenously. Her vital capacity was 1300 cc. She was given 28 mg. of diphenhydramine intravenously, with prompt relief of her dyspnea and a rise in her vital capacity to 2300 cc. Six inhalations of Isuprel (1:200 aerosol) 8 minutes later raised her vital capacity 500 cc. more, even though she was very drowsy at the time. Several minutes later she fell asleep. She experienced no further marked respiratory distress during the remainder of her hospital stay.

Case 7. F. M., a 25-year-old married woman, had a 20-year history of seasonal asthma and hay fever, for which frequent hospital admissions had been required. In addition to eczema in childhood, there was a strong family history of allergy. Skin tests showed marked positive reactions to ragweed and dust. Predictable dyspnea was readily produced in the laboratory with 0.025 mg. of histamine intravenously during her asthma-free intervals.

Although a regimen of oral administration of diphenhydramine and potassium iodide and Isuprel by inhalation kept her comfortable during the entire pollen season, she experienced moderately severe bronchospasm with the onset of the first cold weather, as she had done the year before, when hospitalization had been necessary. After 2 sleepless and distressing nights, during which Isuprel inhalation was required every 30 to 60 minutes and aminophylline suppositories (0.5 gm.) were without appreciable relief, she came to the clinic. Her vital capacity was 700 cc. She was apprehensive, fatigued, tense and in severe respiratory distress. A marked nonproductive cough was present. Isuprel by inhalation was repeated but was again without effect. Diphenhydramine was administered intravenously, and after the injection of 2 cc. (approximately 10 mg.) her dyspnea was greatly relieved. The only side effect noted was slight drowsiness. Ten minutes after diphenhydramine, her vital capacity was 1800 cc. Six inhalations of Isuprel (1:200 aerosol) further increased her vital capacity to 2400 cc.

Hospitalization was probably prevented in this patient by the prompt relief afforded by diphenhydramine and the restoration of sympathomimetic aerosol sensitivity it effected. She also noted, thereafter, that if she took an aerosol of equal parts of 5 per cent tripelennamine and Isuprel (1:200 solution) prior to going out into the cold, the onset of an asthmatic paroxysm, which had been poorly controlled by bronchodilator aerosols alone, was prevented. The efficacy of the rectal

instillation of the aminophylline-diphenhydramine combination was also impressive.

Discussion

In this series of 15 cases of acute bronchial asthma, the intravenous administration of diphenhydramine or tripelennamine resulted in clinical improvement in 10. In some cases marked amelioration of dyspnea directly followed the administration of the antihistaminic agent. In others the effect of the drug was indirect, by enhancing the bronchodilator powers of subsequently administered sympathomimetic drugs ("adrenergic potentiation"). The sedative action ("hyoscine effect") of diphenhydramine especially was also of value.

Several authors have commented upon the efficacy of parenteral administration of antihistaminic agents in asthma. Rosenberg and Blumenthal[28] treated 3 patients with severe acute attacks of bronchial asthma, employing doses of 30 to 40 mg. of diphenhydramine intravenously. Although in 2 cases there was no appreciable change, the third patient exhibited immediate objective relief. Cohen[35] controlled an attack with as little as 8 mg. of diphenhydramine intravenously. However, Jenkins and his co-workers[36] obtained indifferent results from diphenhydramine given intravenously in 8 cases. It has been our experience, particularly in elderly patients with asthma, that when direct relief from the antihistaminic agent is not forthcoming, the restoration of adrenergic response that may follow is often therapeutically important.

It appears, however, that the effectiveness of therapy with these agents is possibly attributable to some other factor than their ability to antagonize histamine. McGavack[37, 38] and others[22, 39] have demonstrated the marked anticholinergic and antibarium chloride action of diphenhydramine, which we have confirmed in asthmatic patients (Fig. 1 and 2) both for this drug and, to a lesser degree, for tripelennamine.[26] Inasmuch as many investigators believe that cholinergic mechanisms in the etiology of asthma and other allergic phenomena are at least as likely as histamine mechanisms,[32, 40, 41] this property assumes considerable possible clinical significance.

Whereas the side effects produced by intravenous injection of antihistaminics are frequently undesirable in the ambulatory patient, drowsiness, relaxation and sleep may be highly desirable in the severely ill patient. Mild drowsiness is also noted after the rectal administration of either agent. We have not observed any significant cumulative effects with parenteral administration of antihistaminic agents. The diminution of expectoration and increase in the tenacity of the sputum that may be observed later have not been troublesome when effective expectorant therapy is also given.

We have found the combination of aminophylline with either diphenhydramine or tripelennamine given rectally two or three times daily to be effective in maintaining many patients after cessation of severe asthma. We have also encountered favorable results in several patients with an aerosol, employing a 2 or 5 per cent tripelennamine solution, or 1.4 per cent diphenhydramine solution, either alone or mixed with equal parts of solutions of sympathomimetic amines. The use of these combinations is particularly effective as a prophylactic measure in patients whose asthma is precipitated by exposure to cold. Feinberg[6] and Arbesman[7] have also noted relief with tripelennamine aerosol in individual patients.

Parenteral antihistaminic therapy is by no means a panacea for the management of the severely ill asthmatic patient, and we have encountered patients in whom no relief was forthcoming from these agents. Waldbott and Young[42] have even observed an aggravation of asthma after the use of antihistaminic agents. This therapy is presented only as an effective adjunct to other proved procedures in the management of the seriously ill patient, with particular emphasis on physiologically directed therapy and "bronchial catharsis.[12, 43, 44] Our poorest results have occurred in patients with obstruction of the tracheobronchial tree by inspissated plugs of mucus, elderly patients with significant and irreversible anatomic disease of heart or lungs and histamine-insensitive persons. The last observation was particularly striking in 2 young patients (B. L. and E. C.) in whom bronchospasm could be induced during clinically asthma-free intervals only by methacholine. Both developed severe bronchial asthma accompanying acute bronchitis and exposure to cold, and required hospitalization. No significant relief was afforded by parenteral administration of antihistaminic agents in either of these patients, even when large doses were given. Of interest in this regard are the observations by Fuchs et al.,[45] who point out that in only 1 of the 23 per cent of their asthmatic patients helped by oral diphenhydramine was organic heart or lung disease present, whereas in the 77 per cent not receiving relief, organic heart or lung disease or an active sinus infection was present in all.

Summary

The relative ineffectiveness of "antihistaminic" agents in severe bronchial asthma when given orally is well known. We have demonstrated prolonged and high degrees of protection against histamine-induced, and to a lesser extent against methacholine-induced, dyspnea and bronchospasm after the intravenous and rectal administration of "antihistaminic" agents in the laboratory. These observations and those of other investigators, indicating that large amounts of histamine may be released in allergic "shock" and hypoxia, and particularly

subsequent to the repeated use of epinephrine, suggested the possible value of these agents in the management of severe bronchial asthma.

Fifteen acutely ill asthmatic patients, 8 in the "intractable" state, were treated and maintained with intravenous, aerosol and rectal administration of diphenhydramine and tripelennamine. The case histories of 7 patients are presented. Significant relief from bronchospasm or the prompt restoration of epinephrine sensitivity followed the intravenous administration of antihistaminic agents in 10 of the 15 patients.

The most favorable therapeutic results were obtained in patients who had previously been found to be "histamine sensitive" during protection studies. The poorest results occurred in patients with obstruction of the tracheobronchial tree by inspissated plugs of mucus, elderly patients with significant and irreversible cardiac and pulmonary disease and histamine-insensitive persons. Many of the patients in this series were satisfactorily maintained during remission with antihistaminic drugs both by the rectal route, alone or combined with aminophylline, and by the aerosol route, alone or combined with a bronchodilator.

Parenteral antihistaminics should be employed only as adjuncts to other effective therapy in the management of the patient acutely ill with bronchial asthma.

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LIVER-FUNCTION TESTS IN ALCOHOLIC PATIENTS*

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IT HAS been believed for decades that chronic alcoholism damages the hepatic parenchyma and may finally lead to cirrhosis of the liver. Available statistics show alcoholism to be an etiologic factor in hepatic cirrhosis in 33 to 87 per cent of the cases. The extent to which the damage to the liver cells caused by alcohol is demonstrable by liver-function tests is of interest. Numerous authors, using the urobilinogen test, the blood bilirubin test, the bilirubin retention test, the bromsulfalein test, the galactose tolerance test and the cephalin-cholesterol-flocculation test found positive results in 20 to 50 per cent of uncomplicated cases of alcoholism. Almost all these reports are based on a relatively small number of cases.

It has been possible to study liver-function tests on a large number of unselected alcoholic patients of the Washingtonian Hospital, an institution specializing in rehabilitation and treatment of male alcoholic patients.

The patients came into the hospital in a state of acute intoxication, some of them after repeated admissions. In only a small percentage of cases was the liver palpable below the costal margin. None of the patients were jaundiced. Delirium tremens was encountered in only 3 per cent of the cases.

In the present study the cephalin-cholesterol-flocculation test of Hanger, the quantitative urobilinogen test in the urine of Wallace and Diamond, the Hay test for cholic acid excretion in the urine and Franke's methylene blue test for bilirubin in the urine were used.

One hundred and forty cephalin-flocculation tests were done on 140 patients with ripened emulsion (Mateer,[1, 2]), and readings were made after twenty-four and forty-eight hours. Twenty-five tests — that is, 17.86 per cent — were + in the forty-eight-hour reading, which is the decisive one; 28 tests, or 20 per cent, were ++ to +++. *In toto*, in 37.8 per cent of examinations, evidence of damage to the liver was demonstrable by the cephalin-flocculation test. These figures are markedly higher than the figure of 20 per cent of positive tests in 40 alcoholic patients found by Wade and Ehrenfest-Richman.[3] However, they stand in good agreement with the figures of former authors, who used various other liver-function tests in alcoholic patients.

The second test used was the quantitative estimation of urobilinogen in the urine (Wallace and Diamond[4]). The test was rated as + when the pink color was still seen in the dilution of 1:3 to 1:15, and as ++ when the color disappeared in dilutions of 1:16 to 1:80. Higher necessary dilutions were recorded as +++.

Examinations of 2308 specimens of urine of 2070 patients gave the following results: in 30.16 per cent, the tests were indicative of liver-cell damage — + in 18.15 per cent, ++ in 9.45 per cent and +++ in 2.56 per cent. These results are in agreement with the figures of positive urobilinogen tests in uncomplicated alcoholism found by other authors.

The largest amounts of urobilinogen seen were 1:300, 1:400, 1:450, 1:540, 1:650 and 1:750. It is surprising that in the cases with +++ reactions an enlarged liver was present in only 33.3 per cent. Serial examinations showed that in all groups considerable variations were sometimes noted from day to day. In 44 cases comparative tests were made of the morning and afternoon specimens. In 43.2 per cent the tests were the same at both times. In 36.3 per cent there was an increase in the afternoon specimen, and in 20.5 per cent there was a slight decrease. The afternoon increase could be as marked as follows: forenoon, ±, afternoon, 1:200, forenoon, 1:50, and afternoon, 1:200.

A comparison of the urobilinogen test and the cephalin-flocculation test made in the same patient shows a good correspondence in 54.64 per cent of the cases. However, it is surprising that in 36.08 per cent the urobilinogen test was positive whereas the cephalin-flocculation test was negative. In only 9.28 per cent the cephalin-flocculation test was positive, and the urobilinogen test negative. The urobilinogen test seems to be more sensitive in acute transient damage to the liver cells, which apparently occurs often in alcoholic patients.

The third test used in this study was Hay's test for cholic acid excretion in the urine. This test is based on the lowering of the surface tension by cholic acids usually measured by the stalagmometric method. Simpler and for practical purposes equally accurate is the Hay test: dried sulfur depuratum powder strewn on the surface of the urine sinks to the bottom of the container when cholic acids are present. Mueller,[5] Lepehne,[6] Doumer[7] and others recommended this test as very useful, though it is not a specific one. I modified the test by acidifying the urine with concentrated hydrochloric acid according to Morrison and Swalm,[8] who recommended the addition of hydrochloric acid for their stalagmometric method. It was found that the Hay test became considerably more sensitive. The test was called ± when a small amount of the sulfur powder sank to the bottom within three to

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five minutes, + when the sulfur powder sank to the bottom immediately but floated in a dilution of the urine with water of 1:1, ++ when the sulfur sank also in the urine diluted 1:1, and +++ when the powder sank in higher dilutions.

Studies of the excretion of cholic acids in the urine of alcoholic patients had the following results: of 660 specimens of urine of 600 patients examined, + tests were found in 13.94 per cent and ++ to +++ tests in 5.46 per cent. That means that liver-cell damage was demonstrable with this test in 19.4 per cent. This number of positive tests is considerably less than the figures of 30.07 per cent positive results with the urobilinogen test and of 37.86 per cent positive tests with the cephalin-flocculation method. Comparison between the cholic acid tests and the urobilinogen tests in these patients reveals equal tests in 77.88 per cent. Surprisingly, the cholic acid test was more sensitive than the urobilinogen test in 14.55 per cent, whereas the urobilinogen test was more sensitive in only 7.57 per cent of the cases.

It is of interest that in nonhabitual drinkers twelve to twenty-four hours after an excess of alcohol the modified Hay test and also the urobilinogen test may become positive. On the other hand Hay tests on approximately 250 patients in my practice and in the Boston Dispensary Medical Clinic with the modified technic showed ± and even + results in patients without apparent liver lesion.

The serial examinations shown in Table 1 may demonstrate the value of the urobilinogen test and the cholic acid test in comparison with the cephalin-flocculation test, the blood bilirubin test, the clinical picture and liver biopsies. This case shows that in the more chronic stage of liver damage the cephalin-flocculation test was still positive while the urobilinogen test and the cholic acid test were negative. The biopsies revealed the severe damage to the liver cells and the fast improvement after modern treatment.

The last test used in these studies was the methylene blue test for bilirubin in the urine (Franke[10]). This procedure is considered as very useful by a great number of investigators, though it is not specific for bilirubin. The technic of Gellis and Stokes[11] was followed. The test was rated as + when blue color appeared with 5 drops; when 6 drops or more were needed the test was rated ++.

Of 150 examined specimens on 150 patients 118 (78.67 per cent) were negative, 12 (8 per cent) were +, and 20 (13.3 per cent) were ++ (6 drops to 10 drops were needed). This means that in 21.33 per cent of the specimens examined slight bilirubinuria as a sign of damage to the liver cells was present although none of the patients had a visible jaundice. The methylene blue test gives almost the same percentage of positive findings in alcoholic patients as the cholic acid test. The comparison of the methylene blue test with the urobilinogen test made in the same patient shows a definite superiority of the latter.

TABLE 1. *Results of Liver-Function Tests in an Alcoholic Patient.**

DATE	UROBILINOGEN	CHOLIC ACIDS	CEPHALIN FLOCCULATION	SERUM BILIRUBIN		REMARKS
				DIRECT	INDIRECT	
			at 48 hr.	*mg./100 cc.*	*mg./100 cc.*	
Nov. 14	+++ (1:650)	+++				
Nov. 15	+++ (1:540)	+++	+++	2.8	3.2	Direct diazo reaction, biphasic, delayed; liver edge extended to navel and was firm, with irregular surface; spleen not palpated; no ascites.
Nov. 18	++ (1:32)	+	++			
Nov. 19	++ (1:16)	+				Liver biopsy† showed acute stage of alcoholic cirrhosis, with marked cellular necrosis and leukocytic reaction (chiefly polymorphonuclears); moderate amount of fat vacuolization; some fibrosis already present.
Nov. 20	+ (1:8)	±				
Nov. 27	±	+	+			
Dec. 4	−	±				
Dec. 20	−	±	++			Liver smaller, not so firm and not tender; second liver biopsy† showed that fat had largely disappeared, and majority of liver cells appeared normal, whereas very few had appeared normal on first examination; polymorphonuclears still present, but markedly decreased in number; fibrosis remained unchanged.

*Treatment consisted of bed rest, high-protein, high-vitamin diet and cholinchloride.
†Performed by Dr. Wade Volwiler.[9]

SUMMARY AND CONCLUSIONS

In studies on large unselected groups of alcoholic patients at the Washingtonian Hospital parenchymal liver damage was demonstrable by the cephalin-cholesterol-flocculation test in 37.86 per cent of 140 specimens examined, by the quantitative urobilinogen test on the urine in 30.15 per cent of 2308 specimens examined, by the methylene blue

test for bilirubinuria in 21.33 per cent of 150 specimens examined, and by the sulfur test for cholic acids in the urine in 19.40 per cent of 660 specimens examined. These figures are consistent with the results of former authors who made various liver-function tests in alcoholic patients, and reveal clearly that there is no regular correspondence between the four tests. In the acute stages the urobilinogen test and the cholic acid test seemed to be more sensitive than the cephalin-flocculation test. Sometimes, the cholic acid test was more sensitive than the urobilinogen test. In the more subacute and chronic stages the cephalin-flocculation test was sometimes the only positive one. A good screening method for office practice to detect early disturbance of the liver is the simultaneous performance of the qualitative urobilinogen test, the modified sulfur test for cholic acids and the methylene blue test for bilirubinuria. The urobilinogen test should be done preferably in the afternoon specimen. Examination showed, confirming numerous previous observations, that in 36.6 per cent of cases the afternoon excretion of urobilinogen exceeded considerably the morning excretion.

Furthermore, it can be concluded that the liver dysfunction in alcoholic patients can be largely transient. Even serious damage as found in the liver biopsy described can subside within a month. The occurrence of marked cirrhosis is surprisingly rare among the patients of the Washingtonian Hospital. This corresponds well with the opinion that hepatic cirrhosis develops only if several different factors have been present. The combination of the modern treatment of alcoholism by the conditioned reflex and psychiatric methods with an early modern anticirrhotic therapy may prevent the development of hepatic cirrhosis in these patients (Thimann[12]).

I am indebted to Dr. J. Thimann, medical director of the Washingtonian Hospital, for giving me the opportunity to make this study, and to Dr. Fred M. Meyer and Mr. J. Stimson for their valuable help in these examinations.

192 Bay State Road

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CONJUNCTIVAL AND CORNEAL CALCIFICATION IN HYPERCALCEMIA*

Roentgenologic Findings

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DEPOSITION of calcium or true ossification in the eyeball has been known to the ophthalmologist and pathologist. These conditions occur most commonly in the choroid and are believed to be often caused by injury. Twining and Shanks[1] distinguished four groups of intraocular calcifications as seen roentgenologically: calcification of the lens, ossification of the vitreous, calcified atheroma of the ophthalmic artery and a shrunken calcified globe. Kautz and Schwartz[2] described, in detail, the x-ray appearance of the ring-shaped calcific deposits in the choroid and also listed and discussed the differential diagnosis of other opacities in the orbit and globe, such as calcium deposits in retinoblastoma in children, opaque and semiopaque foreign bodies, vascular calcifications, phleboliths, orbital angioma and osteoma.

Walsh and Howard[3] have found, by ophthalmologic methods, calcification of the eye in patients with hypercalcemia. In their report, describing their own experience over ten years at the Johns Hopkins Hospital and similar observations by Dr. David Cogan[4] of the Massachusetts Eye and Ear Infirmary, they list 16 cases in which 7 patients presented the clinical picture of hyperparathyroidism, 7 vitamin D poisoning, and 2 sarcoidosis.

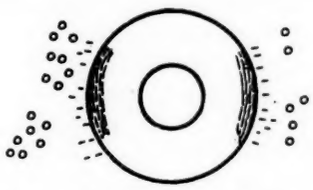

FIGURE 1. *Corneal and Conjunctival Calcifications As Found on Ophthalmoscopic Examination of the Left Eye.*

The lesions, identified with the aid of the slit lamp, are of two distinct types: one in the conjunctiva, and the other in the cornea (Fig. 1). The conjunctival lesions appear as small glass-like particles within the conjunctiva of the palpebral-fissure region. These minute areas are crystal clear. They may be many or few. The second type of ocular abnormality occurs in the cornea. It consists of hazy, grayish, granular epithelial and subepithelial opacities running concentrically with the limbus on either the nasal or the temporal side or both. The opacity is most dense at the periphery, fading out centrally. Its appearance is similar to that of band keratitis seen in association with intraocular inflammation or rarely as a primary disorder. Chemically, these deposits are identified by conjunctival biopsy as probably consisting of calcium phosphate. The roentgenologic visualization of these ocular calcifications is the subject of this report.

CASE REPORT

A. E. S., (B.I.H., M4364),§ a 42-year-old man, had had crippling polyarthritis for 20 years and had received vitamin D medication since 1942, including 2 or 3 Ertron capsules daily, 3 or 4 tablets of Darthronal daily for 6 months and Dolcin tablets for several months. In 1943 a right ureteral colic had occurred, with hematuria and passage of "gravel." There were several similar episodes in the following year. When the patient was seen on January 14, 1949, he complained of a dull pain in the left costovertebral angle and gross hematuria. X-ray examination of the abdomen revealed bilateral calcification of the kidneys. On the basis of the history and these findings he was admitted to the hospital for further study.

Physical examination showed an edentulous patient with moderate pallor of the oral mucosa and the skin. The thyroid gland was enlarged to about three times the normal size and contained several nodules. The chest roentgenograms revealed bilateral changes in both upper lobes, consistent with arrested tuberculosis of the hematogenous type and moderately advanced emphysema. Destructive joint changes consistent with advanced rheumatoid arthritis were found in the fingers, wrists, elbows, shoulders, knee joints, left hip and spine. There was marked generalized decalcification of the bones, especially the long bones, with loosening of the corticalis, but without cyst formation. There was in addition evidence of marked muscular wasting.

The kidneys, which were rather small, were normal in shape and position. There was extensive mottled calcification throughout both kidneys, the individual calcium flecks being 3 mm. and smaller. The distribution of the calcification followed the individual pyramids of the kidney, with less calcification in the left kidney. Intravenous urography and retrograde pyelography revealed delay in excretion, marked impairment of concentration and slight dilatation of the calyxes. These examinations also confirmed the intraparenchymatous location of the calcific deposits. In a complete survey, no soft-tissue calcification was found in the extremities or the walls of the chest and abdomen.

An ophthalmologic consultant reported as follows (Fig. 1):

> There is no redness in either eye. The corneas and conjunctivas look normal microscopically. The anterior chambers, pupils and tensions are normal. The lenses and vitreous are clear. The disks, maculae and retinal vessels appear normal. Vision is about 20/25 in each eye. Slit-lamp examination reveals grayish-white, powdery opacities along the limbus of the cornea, both temporally and nasally, from about 2-5 and 7-10 o'clock. The opacities are not deep, with only rare superficial blood vessels and about 1.5 to 1.0 mm. wide. Otherwise, the corneas are clear.

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§A complete discussion of the metabolic and hormonal aspects of this case will be published elsewhere by Drs. Mark F. Lesses and S. L. Gargill.

The bulbar conjunctivas in the interpalpebral spaces show occasional small, round and oval, glistening superficial, slightly elevated "cysts" or crystals. Some are single and isolated; others are grouped together. In addition to these shiny spots, there are rare nonglistening deposits under the conjunctiva, with no enlargement or newly formed blood vessels. These changes are identical in both eyes. This microscopical eye picture agrees with that described in patients with hypercalcemia.

Examination of the urine showed a +++ test for albumin, with a specific gravity of 1.010; ++ to +++ tests for calcium were repeatedly demonstrated by the Sulkowitch method while the patient received a low-calcium diet. Sputum and urine examinations for tubercle bacilli by smear, culture and guinea-pig inoculations were negative. Morphologic blood studies showed a moderate anemia, with a red-cell count of 3,500,000 and hemoglobin of 10.1 to 12.9 gm. per 100 cc., and were otherwise normal. The nonprotein nitrogen of the blood ranged from 50 to 79 mg. per 100 cc. in 14 examinations. Five total-protein examinations were 6.15 to 7.45 gm. per 100 cc. Seventeen calcium determinations ranged from 10.7 to 11.6 mg. per 100 cc. and dropped to 8.7 to 9.1 mg. per 100 cc. after treatment with stilbestrol, saline infusions and Amphojel. Twelve inorganic serum phosphorus determinations showed values of 4.5 to 4.7 mg. per 100 cc. before treatment and values of 2.9 to 2.3 mg. per 100 cc. after treatment. The alkaline phosphatase ranged from 2.4 to 3.1 Bodansky units.

Skull roentgenograms disclosed faint calcification in annular arrangement in the orbits (Fig. 2). With the bone-free technic,

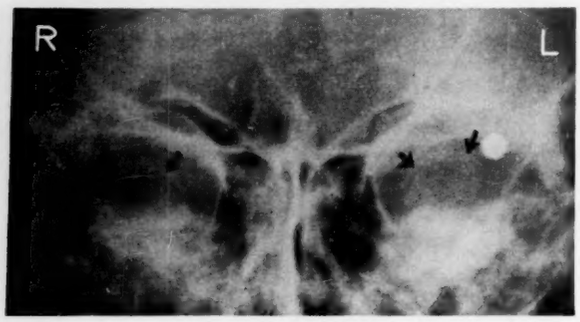

FIGURE 2. *Portion of a Posteroanterior Roentgenogram of the Skull.*

The white, curved lines in the orbits (arrows) represent the corneal calcifications. (The white spot above the left orbit is due to a buckshot beneath the skin.)

described below, these calcifications were brought into better relief. They were of two different types. When the scleral portion of the globe was hit tangentially plump, rod-like calcific deposits 2 mm. in width and 3 or 4 mm. in length in a curvilinear arrangement were seen. If the corneal limbus was hit tangentially a solid, homogeneous, dense calcific

A B

FIGURE 3. *Two Tangential Views of the Left Globe (Bone-Free Technic) Demonstrating the Corneal Calcification* (A) *and the Conjunctival Calcifications* (B). *(The white spot above the left orbit is due to buckshot beneath the skin.)*

shadow of less than 1 mm. in width and 7 mm. in length was seen in the left eye (Fig. 3), and an interrupted similar shadow line 8 mm. in length was seen in the right eye.

In the bone-free technic standard dental films are used. The patient, conveniently seated in a dental chair, presses the film with two fingers of the opposite hand close to his nose in the medial corner of the eye. The tube of the dental x-ray machine is centered toward the external canthus from behind in such a way that the beam covers as much of the eyeball as possible. The patient keeps his eye open and is directed to look steadily alternating to the side, straight forward and medially, in order that several tangential views of various parts of the anterior convexity of the globe may be obtained. The technical factors are the same as those for frontal teeth; 15 MA, 55KV and 1 second were the technical factors used with our equipment.

DISCUSSION

The roentgenologic findings of calcification of the conjunctiva and cornea in the palpebral fissure can easily be correlated with the ophthalmoscopic findings of Walsh and Howard,[3] observed also in the case reported above. Roentgenologically, two types of calcification have been identified. The short, rod-like deposits are apparently identical with the crystal-clear, nodular deposits found in and beneath the conjunctiva; the linear shell-like deposits correspond to the calcification in the limbus. The observations of Walsh and Howard, as well as those of Cogan,[4] were made exclusively in patients with hypercalcemia of various origin.

In this case, too, the ocular calcification is apparently a manifestation of hypercalcemia though the cause of the hypercalcemia is not definitely determined. Three causative factors were considered: hyperparathyroidism, vitamin D poisoning and immobilization due to rheumatoid arthritis.

Widespread metastatic calcifications have been observed in all three of these conditions (Mulligan[5]). However, the calcium deposits in many organs, such as the lung, heart, stomach, liver and spleen, can be recognized only by pathological examination of the tissues. Calcifications of the kidneys, periarticular structures and subcutaneous tissue, as well as arterial calcifications, of diagnostic value solely in young persons, have been the only ones accessible to roentgenologic exploration. Renal and vascular calcifications have been found with great frequency in all three of these conditions, whereas periarticular calcium deposits, rather common in excess of vitamin D, are but rarely reported in hyperparathyroidism and hypercalcemia secondary to bone and joint disease. The generalized moderate decalcification of the bones occurs in all three conditions and has no differentiating significance in the presence of considerable renal damage. Disappearance or marked diminution of massive deposits of lime salts have been observed after withdrawal of vitamin D medication with or without simultaneous reduction of calcium intake (Dan-

owski, Winkler and Peters,[6] McLean and Lebo[7] and Freeman, Roads and Yeager[8]). Similarly, Howard and Meyer[9] noticed a recession of the ocular calcifications in 4 of 8 cases within one to sixteen months of withdrawal of vitamin D, often associated with, but not always parallel to, general clinical improvement.

Dr. Fuller Albright, who saw the patient in consultation, summarized his opinion as follows:

> There are at least three sequences that could have led to the present picture: primary hyperparathyroidism, with hypercalcemia, nephrocalcinosis, renal insufficiency, rising serum phosphorus and falling serum calcium; rheumatoid arthritis, with immobilization, osteoporosis of disuse, hypercalcuria, nephrocalcinosis and so forth; and vitamin D overdosage, with rising serum calcium, nephrocalcinosis and so forth.
>
> The fact that stones antedated vitamin D therapy is against the third sequence and consistent with the first two. The fact that abnormal calcium is confined to the eyes and kidneys is also somewhat against vitamin D overdosage. I favor primary hyperparathyroidism. There is probably little to be gained by total removal of the parathyroid tumor, since the degree of renal insufficiency requires an increased compensatory production of hormone, greater than the tumor is now making. The diagnosis can be made only by exploration.

The patient was explored, but no parathyroid tumor was found in the neck.

Summary

A case of hypercalcemia is reported, the etiology of which is not yet certain. Primary hyperparathyroidism, immobilization secondary to rheumatoid arthritis or vitamin D poisoning possibly played a role in the etiology.

Roentgenologic examination of the anterior portion of the eyeballs revealed calcification of two different types corresponding to the two types described by Walsh and Howard, found by ophthalmoscopic examination, but not yet described in the roentgenologic literature.

The bone-free x-ray technic used in this examination is described in detail.

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AGRANULOCYTOSIS FOLLOWING PYRIBENZAMINE*

Report of a Case

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THE effectiveness of Pyribenzamine (tripelennamine hydrochloride) in many allergic states and its apparent freedom from toxicity have led to its widespread use with little fear of serious reaction. Thus far only 1 case of depression of the granulocytic series after Pyribenzamine therapy has been reported.[1] The following case is believed to represent agranulocytosis resulting from the use of Pyribenzamine over a period of five and a half weeks.

Case Report

A 39-year-old housewife entered the hospital complaining of sore tongue and mouth of 3 days' duration. The past history included migraine headache since the menarche, for which she had frequently used empirin compound. There was no history of eczema, hay fever, asthma or other allergic reactions to foods or drugs until 2 months before admission, when she had noted a red, itching rash on the left forearm spreading to involve the trunk. This rash was diagnosed as a contact dermatitis. Seven weeks before entry she was treated with Benadryl, lotions and salves without effect. Five and a half weeks before admission the hemoglobin concentration was 13.7 gm. per 100 cc., and the blood smear was normal. Medications were changed to Pyribenzamine, 50 mg. three times daily, chloral hydrate for sleeplessness and Ergotrate (ergonovine maleate) for her headaches. On this program the rash and itching subsided. Three and a half weeks before entry the Pyribenzamine dosage was reduced to 25 mg. three times daily.

She had used no medication except Pyribenzamine for at least a week preceding the onset of the present illness. Three days before admission she became ill with mild chills, malaise, generalized aches, prostration, sore mouth and a temperature of 100°F. On the next day she omitted the Pyribenzamine and took several empirin tablets. Two days before admission ulcerations appeared on her tongue, her gums became swollen, and she complained of an unpleasant taste. She had no sore throat. From then until admission the mouth and tongue became progressively more painful, and she took food and fluids with increasing difficulty. Treatment consisted of mouth rinses with salt, sodium bicarbonate and milk of magnesia. On the afternoon of admission the white-cell count was 1700, with 2 per cent neutrophils in the stained smear. She was given 300,000 units of penicillin in beeswax and oil intramuscularly, and was referred to the hospital. During the 5½ weeks preceding her illness, she had taken a total of 4.0

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gm. of Pyribenzamine. She had had a normal menstrual period beginning 2 days before the onset of her illness.

Physical examination showed a well developed and well nourished woman complaining of a sore mouth but appearing only moderately ill. There were two small ecchymotic areas on the lateral surface of the right forearm. There were no petechiae. The eyes, ears and nose were normal, including funduscopic examination. The breath was not remarkable. There was generalized swelling of the gums, with several areas of hemorrhage and necrosis of the papillae. On the sides of the tongue were three deep, punched-out necrotic ulcerations measuring about 5 mm. in diameter and covered with yellow exudate. There was no surrounding inflammation. The pharynx and tonsils were normal. There was an enlarged tender anterior cervical lymph node on the right. The heart and lungs were normal. The liver edge was palpable 4 cm. below the right costal margin in the midclavicular line on deep inspiration, its upper border being in the sixth interspace, to percussion. It was nontender. The tip of the spleen was felt below the costal margin on deep inspiration. The extremities were normal. Neurologic examination revealed no abnormalities.

The temperature was 102°F., the pulse 112, and the respirations, 18; the blood pressure was 118/70.

The urine was yellow, acid and clear, with a specific gravity of 1.020, and with negative tests for albumin, sugar, bile and acetone. Microscopical examination of the sediment showed normal results. A stool was brown and guaiac negative. A blood nonprotein nitrogen taken on the 2nd hospital day was 29 mg. per 100 cc. The blood Hinton and Kahn tests were negative. A heterophil-antibody agglutination on the 3rd hospital day was negative in all dilutions. The prothrombin time was 16.7 seconds, with a control of 15.0 seconds. Four hemoglobin determinations (Sahli) ranged from 13.4 to 16 gm. per 100 cc. Four red-cell counts ranged from 4,180,000 to 4,500,000. The platelets were normal. The white-cell count on the evening of admission was 3200, with but 8 per cent neutrophils and 6 per cent band forms. On the next day the white-cell count had risen to 5300, with 24 per cent neutrophils. Thereafter the total neutrophil count rose as shown in Table 1.

The patient received intramuscular injections of penicillin in doses of 100,000 units every 3 hours for 6 days, and 100,000 units every 8 hours for a total dosage of 4,800,000 units. Supportive treatment included a soft diet and 2 multivitamin capsules daily. On the 3rd hospital day folic acid, 10 mg. daily, was added. The patient was febrile for the first 2 hospital days, the temperature reaching 101.4°F. on the 2nd day, after which it remained normal. This fall in temperature was paralleled by a decrease in the pulse rate and coincided with marked improvement in the general well-being of the patient. The lesions in the mouth healed slowly but steadily so that at discharge, 8 days after admission, the gums were virtually normal and the ulceration on the tongue was clean, with epithelializing, small concavities. The spleen receded on about the 4th hospital day.

Examination two months after the acute illness revealed irregular depressions at the sites of the former ulcerations on the tongue. The spleen was not palpable. The liver was not enlarged. The patient was asymptomatic and had refrained from using any medication. The red-cell count was 4,630,000, with a hemoglobin of 14.3 gm., and the white-cell count 8700, with 73 per cent neutrophils, 20 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils.

Discussion

During the five and a half weeks preceding her illness the patient had taken four medications: Pyribenzamine, Ergotrate, empirin compound and chloral hydrate. However, for a week or more before the onset of her illness, she had used nothing but Pyribenzamine, omitting the others because she felt so well. She did not use empirin again until a day after the onset of her sore mouth, when she omitted Pyribenzamine for the first time in five and a half weeks after having taken a total of 4.0 gm. of the drug. On the basis of the history, Pyribenzamine seems to be incriminated. The depression of the granulocytes that occurred in this case only after prolonged exhibition of the Pyribenzamine seems analogous to the leukopenia seen after extended use of other drugs, such as the sulfonamides, thiouracil or propylthiouracil. In all these agents the effect on the granulocytic series is not manifest in the early days of the administration of the drug. Wintrobe[2] states that the granulocytopenia from sulfanilamide usually occurs after one to three weeks of treatment, and that from thiouracil usually after four to eight weeks. It seems that the analogous time for Pyribenzamine is four to five weeks. In the case previously reported[1] granulocytopenia occurred after eight weeks of Pyribenzamine.

Table 1. *Effect of Therapy on Neutropenia in a Case of Agranulocytosis Following Pyribenzamine.*

Day	Treatment		White-Cell Count	Neutrophils	Band Forms	Lymphocytes	Monocytes	Eosinophils	Basophils	
	penicillin units/day	folic acid mg./day		%	%	%	%	%	%	
1	—	—	1,700	2	—	—	98	—	—	
1	600,000	—	3,200	8	6	34	52	—	—	
2	800,000	—	5,300	24	—	50	24	2	—	
3	800,000	10	4,400	34	—	44	22	2	—	
4	800,000	10	6,000	57	2	28	12	1	2	
5	800,000	10	5,300	56	—	32	7	—	—	(Myelocytes, 4%; metamyelocytes, 1%.)
6	400,000	10	6,300	56	11	23	6	1	—	(Myelocytes, 2%; metamyelocytes, 1%.)
7	300,000	10	5,600	62	1	30	5	2	—	
8	300,000	10	7,500	70	—	27	3	—	—	
0	—	—	7,600	75	1	19	5	1	—	

Although folic acid was used in therapy, we do not believe that it played a role in recovery, since the rise in the white-cell count had begun before folic acid was started. The significant monocytosis observed initially and in subsequent examinations (Table 1) may be considered evidence of the onset of spontaneous recovery, according to the observations of Reznikoff.[3]

Thompson[4] reported cyclic neutropenia just preceding the menstrual flow, and he believed that the

onset of menstruation was a predisposing factor in the precipitation of agranulocytosis. In the case reported above, it is interesting that the acute symptoms began two days after the beginning of the period.

Summary

A case representing agranulocytosis following pyribenzamine is presented. This is the second case report of this condition subsequent to the administration of Pyribenzamine and calls attention to the advisability of performing white-cell counts on any patient receiving Pyribenzamine for prolonged periods who shows signs or symptoms of agranulocytosis.

Since the preparation of this report Drs. George A. McCormack and Richard G. Whiting have informed us of a similar case treated at the Lawrence Memorial Hospital in Medford. Their patient took approximately 400 mg. of Pyribenzamine for a month prior to the onset of agranulocytosis. On the sixth day after the onset of this patient's illness the white-cell count had declined to 1100, and the neutrophils had completely disappeared. The patient made an uneventful recovery.

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MEDICAL PROGRESS

RH AND OTHER BLOOD GROUPS*

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THE Rh and other blood groups have achieved great importance in the last few years because of their relation to erythroblastosis fetalis. But numerically this disease may not emphasize the need for practical knowledge about blood groups as often as blood transfusion does — a therapeutic procedure that has become relatively simple and used, or sometimes possibly abused, probably several million times a year. In addition, genetic and anthropologic studies using blood-group characteristics have been revitalized by the discovery of the newer and now much more numerous blood agglutinogens. And finally, medicolegal problems, which formerly were unsolvable because of too few positive detectable characteristics for identification of any person's blood-group individuality, can now come closer to satisfactory resolution because of the possible permutations and combinations of the blood-group factors, making any blood more nearly unique.

By use of knowledge and technics now available, the safety of multiple transfusion of whole blood has been greatly increased. Relatively simple laboratory tests are now available to establish accurately the compatibility of the blood of the donor and the recipient.

The discovery of the Rh factor in 1939 by Levine and Stetson,[1] who found the Rh antibody in a parturient woman after a hemolytic transfusion reaction, and independently in 1940 by Landsteiner and Wiener,[2] who found the Rh antibody in a rabbit immunized by Rhesus-monkey blood, opened the door to re-exploration of blood groups. This subject has been reviewed recently.[3-6] Seven different blood-group systems are now known in which the antigens are common enough to be useful in such studies, and these seven systems are probably controlled by seven different pairs of chromosomes.

This report briefly reviews the field of blood groups, giving only the basic information. The blood-group antigens and antibodies are discussed briefly, with emphasis on genetic and immunologic factors. Certain important clinical considerations will be discussed in relation to some of the antigens. The paragraphs on technic are brief. More complete studies have been published elsewhere.[3-9] A later review will cover the clinical aspects of the subject.

Antigens and Antibodies of Human Blood Groups

The blood groups are named for the specific antigenic substances (agglutinogens) in the red blood cells. These antigens are inherited factors, appearing early in fetal life and remaining unchanged throughout life. Table 1 lists most of the known antigens that are recognizable in the blood groups and subgroups. Certain rare antigens, and identifiable variants other than those listed below in-

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crease the number of possible genotypes* to well over 100,000,000.

The ABO System

Antigens. The A_1, A_2, B and O antigens are inherited as Mendelian alleles. The A and B antigens of the red cells were discovered by Landsteiner[10] fifty years ago. That O is actually an antigen has only recently been recognized.[11] The variant A_2 has been known for many years.[12] The curious facts that virtually all B-negative adults have anti-B antibodies and that virtually all A-negative adults have anti-A antibodies in their serum have not been explained on either genetic or immunologic grounds, but they are obviously of enormous importance as far as blood transfusions are concerned. The specificity of anti-B is quite uniform from one person to another, but there is considerable variation in anti-A antibodies, their activity against A_2 cells often being weak. Occasionally, anti-A_1 is found in the serum of an A_2 person.[8] An antibody that agglutinates all O and A_2 red cells has been variously called "anti-O" and "anti-A_2"; its exact significance is a matter of dispute. The relations between the antigens and antibodies in the ABO system are shown in Table 2.

TABLE 1. *Known Antigens of Seven Different Systems of Blood Groups.**

ANTIGENS	SYSTEM	PRESENTLY IDENTIFIABLE PHENOTYPES†	POSSIBLE GENOTYPES
A_1, A_2, B, O‡	ABO	6	10
§{C, C^w, c D, d E, e	Rh	36	78
§{M, N S	MNS	6	10
P	P	2	3
Le^a, Le^b	Lewis	3	3
K, k	Kell	3	3
Lu^a	Lutheran	2	3
Totals: 20 antigens, 7 systems		46,656	631,800

*A number of variants are omitted.

†Phenotype: the identifiable antigenic makeup of the red blood cells, dependent on, but not necessarily indicating, the complete gene pattern.

‡Antigens shown in the same line are mendelian allelomorphs (alternative characters).

§Antigens in brackets are genetically linked.

The A and B antigens are rather widely distributed in nature, especially A, which is found in various animals and plants. Both antigens are easily obtainable in pure water-soluble form from extra-human sources (for example, A is obtained in high concentration from hog gastric mucosa) and have been used in concentrated solution for experimental purposes or for the neutralization of anti-A and anti-B in human whole blood or serum.[13] The A and B antigens are also found, in various amounts, in other human tissues than the red cells. Persons who have large amounts of the antigens A or B, or both, in their saliva and gastric juice are called "secretors," and inherit this characteristic as a Mendelian dominant. Eighty per cent of Europeans are secretors.

Antibodies. Anti-A and anti-B antibodies are naturally occurring substances. They agglutinate red cells containing the corresponding specific antigens. Agglutination does not require complement, is most active at 4°C., is active at 37°C. and occurs with red cells suspended in saline solution, serum or a solution of albumin.

Isohemolysins and isoagglutinins may occur in the same serum. They are not separable, and differ in that hemolysis requires serum complement. Isoagglutinins are accompanied by isohemolysins in only about 30 per cent of possible cases.[8] They are specifically neutralized by soluble A or B substance.

TABLE 2. *Simplified Summary of ABO System.**

BLOOD GROUP (ANTIGENS OF RED CELL)	FREQUENCY OF BLOOD GROUPS IN UNITED STATES	ISOAGGLUTININS IN SERUM†	RED CELLS THAT ARE AGGLUTINATED AND MAY BE HEMOLYZED BY SERUM
	%		
O	45	anti-A and anti-B	Groups A, B, and AB
A	41	anti-B	Groups B and AB
B	10	anti-A	Groups A and AB
AB	4	—	—

*The phenotypes and genotypes are summarized in Table 3.

†Isohemolysins may be present.

TABLE 3. *The ABO System.*

PHENOTYPE	OBSERVED FREQUENCY IN UNITED STATES*	GENOTYPE	CALCULATED FREQUENCY†	REACTIONS WITH TYPING SERUMS		
	%		%	*anti-A*	*anti-A_1*‡	*anti-B*
A_1	41.0	A_1/A_1	3.53	+	+	0
		A_1/A_2	2.56	+	+	0
		A_1/O	25.30	+	+	0
A_2		A_2/A_2	0.46	+	0	0
		A_2/O	9.15	+	0	0
A_1B	4.0	A_1/B	2.94	+	+	+
A_2B		A_2/B	1.06	+	0	+
B	10.0	B/B	0.72	0	0	+
		B/O	9.28	0	0	+
O	45.0	O/O	45.00	0	0	0

*Data of Snyder[14] on 20,000 Americans.

†Subgroups of ABO system based on Wiener's[8] tests of 1077 white persons (New York).

‡Anti-A serum absorbed with A_2 cells.

Immune anti-A and anti-B. There is no evidence that natural anti-A or anti-B harms the fetus. In contrast to the natural anti-A and anti-B antibodies, "immune" antibodies have been described by Witebsky[5] and found in numerous cases, as in a Group A or Group O woman carrying a Group B fetus. The immune anti-A or anti-B gives a

*Genotype is defined as the total gene pattern, inherited from the parents, not necessarily identifiable by typing serums.

higher titer in serum medium than in saline solution or in albumin and is difficult to neutralize with soluble antigen.[5] The immune anti-A antibodies so far described have been much more active against A_1 than against A_2 cells. A small proportion of the cases of erythroblastosis fetalis are caused by immune anti-A or anti-B, but it is definitely known that the Group A or O mother of a Group B fetus can have immune anti-B in her serum without any observable ill effects on the baby.

Anti-A and anti-B typing serums. The apparent discrepancy between the number of identifiable phenotypes and known genotypes in the ABO system (Table 3) is explained by the limited number of specific antiserums as follows. Anti-A serum agglutinates all Group A and Group AB cells. Anti-A_1 (anti-A serum absorbed with A_2 cells) does not agglutinate A_2 or A_2B cells, but does agglutinate A_1 and A_1B cells. Anti-B serum agglutinates only B and AB cells. The person of genotype A_1A_2 can be differentiated only by family studies, not by direct testing, from the A_1A_1 or A_1O person, and all three have therefore the same phenotype. Likewise, the genotype BB cannot be distinguished serologically from the genotype BO.

The CDE (Rh) System

Seldom has a subject caused so much confusion in the minds of both physicians and laity as that of the Rh factor. Much of the confusion appears to result from the rapidity of progress in the field and from the complex terminology. The antigens and antibodies are not confusing if they are considered one by one, employing the nomenclature of Fisher and Race, which is based on assigning letters (C, D, E, c, d, e) to the specific antigens of the Rh system (Table 4). Although it is recommended that the CDE nomenclature be adopted as standard,[17] the Wiener abbreviations are indispensable in conversation, and must be known if much of the literature is to be understood.

Genetics of the CDE system. According to Fisher's theory there are three sets of allelic (alternative) genes, C, C^w, and c, D and d, E and e — one set for each of three loci in one of the pairs of chromosomes. The loci are closely, or absolutely, linked,

TABLE 4. *The Rh System.*

Subgroups Among British Population*		Genotypes Among British Population*			Agglutination by Antiserums					
Wiener nomenclature	Frequency	(Fisher-Race)	(Wiener modified)	Calculated frequency	*anti-C* (*anti-Rh'*)	*anti-D* (*anti-Rh'$_0$*)	*anti-E* (*anti-Rh''*)	*anti-c* (*anti-Hr'*)	*anti-d* (*anti-Hr$_0$*)	*anti-e* (*anti-Hr''*)
	%			%	70%	85%	30%	80%	63%	97%
rh	15.1	cde/cde	r r	15.1020	0	0	0	+	+	+
rh'	0.8	Cde/Cde	R' R'	0.0097	+	0	0	0	+	+
		Cde/cde	R' r	0.7644	+	0	0	+	+	+
Rh$_0$	2.1	cDe/cDe	R$_0$ R$_0$	0.0659	0	+	0	+	0	+
		cDe/cde	R$_0$ r	1.9950	0	+	0	+	+	+
rh''	0.9	cdE/cdE	R'' R''	0.0141	0	0	+	+	+	0
		cdE/cde	R'' r	0.9235	0	0	+	+	+	+
Rh$_1$	53.4	CDe/CDe	R$_1$ R$_1$	17.6803	+	+	0	0	0	+
		CDe/Cde	R$_1$ R'	0.8270	+	+	0	0	+	+
		CDe/cDe	R$_1$ R$_0$	2.1585	+	+	0	+	0	+
		CDe/cde	R$_1$ r	32.6808	+	+	0	+	+	+
		Cde/cDe	R' R$_0$	0.0505	+	+	0	+	+	+
Rh$_2$	14.1	cDE/cDE	R$_2$ R$_2$	1.9906	0	+	+	+	0	0
		cDE/cDe	R$_2$ R$_0$	0.7243	0	+	+	+	0	+
		cDE/cdE	R$_2$ R''	0.3353	0	+	+	+	+	0
		cDE/cde	R$_2$ r	10.9657	0	+	+	+	+	+
		cDe/cdE	R$_0$ R''	0.0610	0	+	+	+	+	+
rh'rh'	0.03	CdE/CdE	R$_y$ R$_y$	0.0000003	+	0	+	0	+	0
		CdE/Cde	R$_y$ R'	0.0001	+	0	+	0	+	+
		CdE/cdE	R$_y$ R''	0.0001	+	0	+	+	+	0
		CdE/cde	R$_y$ r	0.0039	+	0	+	+	+	+
		Cde/cdE	R' R''	0.0234	+	0	+	+	+	+
Rh$_1$Rh$_2$	13.6	CDE/CDE	R$_z$ R$_z$	0.0006	+	+	+	0	0	0
		CDE/CDe	R$_z$ R$_1$	0.2048	+	+	+	0	0	+
		CDE/cDE	R$_z$ R$_2$	0.0687	+	+	+	+	0	0
		CDE/CdE	R$_z$ R$_y$	0.00002	+	+	+	0	+	0
		CDE/Cde	R$_z$ R'	0.0048	+	+	+	0	+	+
		CDe/CdE	R$_1$ R$_y$	0.0042	+	+	+	0	+	+
		CDE/cDe	R$_z$ R$_0$	0.0125	+	+	+	+	0	+
		CDe/cDE	R$_1$ R$_2$	11.8648	+	+	+	+	0	+
		CDE/cdE	R$_z$ R''	0.0058	+	+	+	+	+	0
		cDE/CdE	R$_2$ R$_y$	0.0014	+	+	+	+	+	0
		CDE/cde	R$_z$ r	0.1893	+	+	+	+	+	+
		CDe/cdE	R$_1$ R''	0.9992	+	+	+	+	+	+
		cDE/Cde	R$_2$ R'	0.2775	+	+	+	+	+	+
		CdE/cDe	R$_y$ R$_0$	0.0003	+	+	+	+	+	+

*Based on data of Race et al.[15] (the frequency of the R_y gene is taken as 0.00005) and Fisher and Race[16] (the frequencies are approximately the same for American whites, the proportion of D-negatives being a little lower — approximately 15 per cent).

and crossing over has not yet been observed. The number of possible combinations that may occur is quite large (Table 4). The genes are given the same names as the antigens of the red cells. It is important to emphasize that the inheritance of these genes is as though they were all *mendelian dominants*. To state it more correctly, there is *no dominance*.

The C^w antiserum[18] and the genotypes having this antigen have not been included in Table 4, since they are of no real clinical importance and their inclusion would complicate the table. The C^w antigen is an uncommon, but serologically and genetically distinct, variant of C. The antigens C, C^w and c are genetically related in the same way that A, B and O are related, as Mendelian allelomorphs. Therefore, all human beings can be divided into six genotypes — CC, CC^w, Cc, C^wC^w, C^wc and cc. It is only when the possible combinations at the C locus are multiplied by the possible combinations at the D locus (DD, Dd and dd), and then by the possible combinations at the E locus (EE, Ee and ee) that the system appears complicated.

Only when it becomes important to determine whether a person is homozygous for D (DD) or heterozygous (Dd) is it necessary to consider the Rh antigens as a group. This is necessary because no anti-d typing serum is available. Anti-C, anti-D, anti-E and anti-c serums are generally available, and can be used to determine with fair accuracy the "zygosity" for D of any given person. A brief examination of Table 4 will indicate how this is done. Predictions must be based on the statistical table unless blood relatives of the person in question are available for examination.

Immunologic considerations of the CDE (Rh) system. The antigens in the Rh system vary considerably in their antigenicity. Only D is a really effective antigen. Between 50 and 75 per cent of D-negative human beings develop immune anti-D antibodies if the attempt at immunization is sufficiently prolonged. About 50 per cent are immunized by a single transfusion of D-positive blood. About 5 per cent are immunized by pregnancies involving D-positive fetuses. The corollary to this last statement should be emphasized — namely, that *95 per cent of D-negative women with D-positive husbands (and D-positive fetuses) are never immunized (sensitized) to D*; their infants will *not* have erythroblastosis.

The *other antigens* of the Rh system are very much less antigenic, although antibodies to each of them have been found in human serums at one time or another. A still unexplained phenomenon is the frequent occurrence of anti-C in a human serum that also contains anti-D, and the extreme rarity of occurrence of anti-C in the serum of a D-positive, C-negative person. This phenomenon suggests some basic immunologic relation between the antigens D and C, so that the presence of the D antigen is protective against immunization to the C antigen. There is a similar, but less striking, relation between anti-D and anti-E antibodies, in that anti-E has been found in many D-positive, E-negative persons (though is most cases it is present along with anti-D), suggesting that the immunologic relation between D and E is less close than that between D and C. The relatively close relation of D to C has been postulated by Fisher on genetic grounds also. It is evident that the protective effect of the D antigen is not shared by either C or E, since D-negative persons having C or E or both appear to be as readily immunized by D as persons lacking both C and E. This problem deserves further study.

The over-all relative effectiveness of the Rh antigens is indicated by the fact that of all persons immunized by one or more of the Rh antigens, over 95 per cent have anti-D, a few have anti-c or anti-E, or both, and an extremely small fraction have anti-C alone, or anti-e or anti-d.

The D *antigen*, besides being the most important from the immunologic viewpoint, is also most variable. D-positive red cells from most persons are agglutinated by all anti-D typing reagents. About 1 per cent of D-positive red cells, however, are agglutinated by some anti-D serums and not by others. This 1 per cent comprises an apparently unlimited variety of peculiar D antigens. The symbol D^u has been given to this group of irregular D antigens,[19] although the single symbol does not imply any specific immunologic or genetic characteristic of the antigen. Since the D^u variants are antigenic, they are clinically important, especially because they are difficult to recognize by routine typing methods. A fatal hemolytic transfusion reaction has resulted from the administration of such blood, thought to be D-negative, to a D-negative person who had previously been immunized by D. The D^u variants are inherited just as the other antigens of the Rh system are, and "breed true" genetically. The D^u antigens are, for clinical purposes, best considered as identical with the D antigen.

The D antigen has been demonstrated with certainty only in the red blood cells and in red-cell stroma. Experiments indicating that D is present in certain other body cells or fluids have not been confirmed.

The antibodies of the CDE (Rh) system. Isoagglutinins for the Rh factors *do not occur naturally*. When found in human serum, they result from active *isoimmunization*, either by transfusion of blood or by pregnancy. Anti-Rh isoagglutinins are developed apparently without anti-Rh hemolysins. Anti-D antibody can be produced artificially in rabbits and some other animals by injection of Rhesus blood or human D-positive blood, but Rh antibodies other than anti-D have not been produced in animals.

In this discussion of the peculiarities of the Rh antibodies, specific reference is made only to anti-D, since other antibodies in this group may behave in a similar fashion.

An important contribution to the science of immunology was made by workers in the field of blood grouping when it was shown that agglutinins existed in different forms. It was first shown that certain anti-D antibodies might specifically coat D-positive cells, without agglutinating them, to such an extent that the coated cells could not then be agglutinated by potent anti-D agglutinating antibodies.[20, 21] Next, it was demonstrated that these antibodies, which were unable to agglutinate red blood cells in saline solution, the traditional medium for such tests, were able to agglutinate red cells in a medium of 20 per cent albumin.[22] Finally, it has been shown that albumin-active (saline-inactive) antibodies exist that are not "blocking" antibodies. This last type of antibody, representing perhaps a third "order" of antibodies, which coat but do not block red cells and do not agglutinate in saline solution, have been called "cryptagglutinoids"* by Hill, Haberman and Guy.[23] Preliminary research by these authors[23] appears to show that the three "orders" of antibody are found in highest concentrations in three distinct protein fractions — gamma globulins (saline-active agglutinins), beta globulins (the albumin-active cryptagglutinoids), and euglobulins (blocking antibodies and cryptagglutinoids). "Agglutination" of red cells is observed, however, with all three "orders" of antibody, in saline solution, when the Coombs technic, using anti-globulin serums, is employed. The several varieties of anti-D antibodies are all specific in their relation to the D antigen and may all be present in the same serum. Their differences only accentuate the need for identifying them in serums presented for investigation. The in vitro activity of anti-D antibodies depends not on any quality of the particular D antigen involved, but solely on the antibody-forming mechanism of the sensitized person.

It is also suggested that the saline-active antibody cannot pass through the placenta, whereas the hyperimmune antibody readily passes through, to be found in the baby's serum (in the case of a D-negative baby) in concentration equal to that in the mother's serum.

The MNS System

The M and N antigens (mendelian alleles) were discovered by Landsteiner and Levine[24, 25] in 1927. The S antigen is a recently discovered one[26] that is genetically linked to M and N. Since each of the three MN types may be positive or negative with respect to anti-S, there are six phenotypes, when anti-M, anti-N and anti-S are all used. Since an anti-s serum has not been discovered, the SS genotype can be distinguished from the Ss genotype only by family studies. Even if anti-s were available, one could not distinguish except by family studies the two genotypes MS/Ns and Ms/NS (Table 5).

In human beings M, N, and S are relatively poor antigens. Natural anti-M and anti-N are observed occasionally in low titer. Such antibodies are usually, if not always, agglutinins effective in the cold. Immune anti-M has been found in a number of cases in which Type N persons have been given transfusions of M or MN blood. The immune anti-M is active at 37°C., and may be the cause of a severe hemolytic transfusion reaction. Anti-S has not been identified as a natural agglutinin, and has not been produced in animals. Several examples of immune anti-S in S-negative persons have been reported. In one such case the antibody failed to cause agglutination of S-positive cells, but did "coat" them as could be demonstrated by the Coombs test. Anti-M and anti-N typing serums are obtained by immunization of rabbits with human Type M and Type N blood.

TABLE 5. *The MNS System.*

Phenotype	Observed Frequency in England*	Genotype	Calculated Frequency	Reactions with Typing Serums		
	%		%	*anti-M*	*anti-N*	*anti-S*
MS	20.9	MS/MS	6.53	+	0	+
		MS/Ms	14.26	+	0	+
Ms	7.41	Ms/Ms	7.74	+	0	0
MNS	28.3	MS/NS	4.15	+	+	+
		MS/Ns	19.68	+	+	+
		Ms/NS	4.52	+	+	+
MNs	22.1	Ms/Ns	21.45	+	+	0
NS	6.9	NS/NS	0.66	0	+	+
		NS/Ns	6.24	0	+	+
Ns	14.5	Ns/Ns	14.78	0	+	0

*Based on data of Pickles[27] in a study of 340 English bloods.

Since clinical problems involving M, N and S are so uncommon, typing with anti-M, anti-N and anti-S is not necessary in routine examinations, although they must be kept in mind whenever clinical problems cannot be solved with the use of A, B and Rh serums.

The P System

The antigen P was discovered by Landsteiner and Levine[25] in 1927 when they found in the serum of a rabbit, immunized with human blood, an antibody that agglutinated about 75 per cent of all human red cells irrespective of their ABO and MN blood groups (Table 6).

No serum corresponding to the predicted anti-p has as yet been identified.

Anti-P is reported to be fairly frequent in P-negative human beings, as a naturally occurring weak

*Other synonyms are hyperimmune antibodies, incomplete antibodies, glutinins and "blockers." Saline-active antibodies are also known as early immune antibodies, complete antibodies and agglutinins.

cold agglutinin. Immune anti-P has been reported, but is very rare. The P antigen is therefore of almost no clinical importance. Potent anti-P typing serum has occasionally been obtained from animals, but is not generally available. Most anti-P serums are more active at 4°C. than at higher temperatures.

TABLE 6. *The P System.*

PHENOTYPE	OBSERVED FREQUENCY IN UNITED STATES*	GENOTYPE	CALCULATED FREQUENCY	REACTIONS WITH TYPING SERUM
	%		%	*anti-P*
P-positive	71.4	P/P	21.6	+
		P/p	49.8	+
P-negative	28.6	p/p	28.6	0

*Based on data of Sanger[28] on 140 Harvard Medical School students and Children's Hospital personnel (1948).

The Le (Lewis) System

The antigen Le^a was originally described by Mourant[29, 30] and called "Lewis." Andresen,[30] in an independent publication, picked the letter L. Andresen also identified Le^b, as a mendelian allele of Le^a, by means of a human serum antibody discovered in his laboratory. Mourant's original "anti-Lewis" (anti-Le^a) agglutinated only the cells of homozygotes (Le^aLe^a), about 20 per cent of the population. Anti-Le^b agglutinates about 80 per cent of all cells, missing all those positive with the original "anti-Lewis" (anti-Le^a). A few persons are negative to both anti-Le^a and anti-Le^b, indicating the probable existence of a third, fairly common allele at this locus. Anti-Le^a, and anti-Le^b serums that we have seen have been more active at cooler temperatures (4 to 20°C.). So far, no clinical problems have arisen with respect to the Lewis antigens. Most, if not all, of the anti-Lewis antibodies so far identified have apparently been natural agglutinins (Table 7).

TABLE 7. *The Le ("Lewis") System.*

PHENOTYPE	OBSERVED FREQUENCY IN UNITED STATES*	GENOTYPE†	REACTIONS WITH TYPING SERUMS	
			anti-"Lewis" (anti-Le^a)	*anti-Le^b*
	%			
"Lewis"-positive, Le (a+b−)	20.5	Le^a/Le^a	+	0
"Lewis"-negative, Le (a−b+)	79.5	Le^a/Le^b	0‡	+
		Le^b/Le^b	0	+
Le (a−b−)		?	0§	0§

*Data of Sanger (Cited by Race et al.[29]) on 132 Harvard medical students and Children's Hospital personnel.

†Le^a = "Lewis" (Mourant) = L_1 (Andresen); Le^b = L_2 (Andresen).

‡Available anti-Le^a serums fail to agglutinate cells of heterozygotes; therefore, Le^a-positive cells are probably homozygous.

§Approximately 5 per cent, in a limited series.

The K ("Kell") System[31]

An antibody active against the red cells of about 11 per cent of the population was first described in England in 1946. This antibody was found in the serum of a woman who had given birth to a baby with erythroblastosis fetalis. The antigen identified by this antibody was named "Kell" from the name of the woman in whose serum it was found. Since the first example in England, a fairly large number of other examples of this antibody have been found in this country and abroad. Anti-Kell has been formed in a Kell-negative person by injection of Kell-positive blood. Some of the examples of anti-Kell serums so far identified have been hyperimmune blocking antibodies, comparable to anti-D. The Kell antigen is thus of some clinical importance. A new antibody, identifying the allele of the Kell factor, has recently been described by Levine et al.[32] and called "anti-Cellano" (Table 8).

TABLE 8. *The K ("Kell") System.*

PHENOTYPE	OBSERVED FREQUENCY	GENOTYPE	CALCULATED FREQUENCY*	REACTIONS WITH TYPING SERUMS	
	%		%	*anti-K*	*anti-k*
KK	10.17†	K/K	0.27	+	0
Kk	99.8*	K/k	9.90	+	+
kk		k/k	89.83	0	+

*Data of Levine et al.[32] (Anti-k = anti-Cellano.)

†Data of Sanger et al.[31]

The Lu ("Lutheran") System

Antibodies identifying a seventh unrelated blood group system (Table 9) were first found by Callender and Race[18] in England. About 8 per cent of red cells of Britishers are agglutinated by anti-Lutheran (anti-Lu^a). Anti-Lutheran has been found in the serum of Lutheran-negative recipients deliberately transfused with Lutheran-positive blood.[33] The antibodies were active in saline solution at 37°C.

TABLE 9. *Lu ("Lutheran") System.*

PHENOTYPE	OBSERVED FREQUENCY IN ENGLAND*	GENOTYPE	CALCULATED FREQUENCY	REACTIONS WITH TYPING SERUM
				anti-Lutheran (anti-Lu^a)
	%		%	
Lutheran-positive Lu (a+)	8.0	Lu^a/Lu^a	0.2	+
		Lu^a/Lu^b	7.8	+
Lutheran-negative Lu (a−)	92.0	Lu^b/Lu^b	92.0	0

*Data of Callender and Race[18] on 582 English bloods.

but were invariably in low titer. Hemolytic transfusion reactions have not been reported as the result of sensitization to the Lutheran antigen, nor has it been found responsible for any cases of erythroblastosis fetalis.

Summary of the Blood-Group Antigens

Seven different, genetically unrelated and immunologically distinct blood-group systems have been well established in human beings. Other antigens have been identified by occasional serums without sufficient study being possible for definite characterization, because of lowness of titer of the antibody, or rarity of the antigen. Many more, undoubtedly, are waiting to be identified. Of all the antigens described, only A, B and D are of enough clinical importance to warrant routine procedures concerning them — A and B because natural antibodies are universal in human beings lacking the antigens in their red cells, and D because of its considerable antigenicity and the consequent danger of transfusion reactions or erythroblastosis fetalis, or both, when D-negative persons are exposed to D-positive blood.

(*To be concluded*)

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Correction. In the article by Drs. Robert S. Schwab and William R. Tillmann entitled "Artane in the Treatment of Parkinson's Disease," which appeared in the September 29 issue of the *Journal*, the sentence beginning "The effect of other antihistaminic drugs . . ." on page 485, immediately before the summary, should be changed to read "The effect of other antihistaminic drugs, such as Thephorin, aminophylline and Benadryl mixtures and compounds (Dramamine), is in the process of evaluation."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35481

PRESENTATION OF CASE

A six-and-one-half-year-old boy was admitted to the hospital because of rapid weight gain, growth of pubic hair and enlargement of the penis.

On routine examination nine months before admission, he had been found in good health, with normal development, weighing 44 pounds. The blood pressure was 100 systolic, 60 diastolic. The genitalia were noted as normal. Approximately six months before admission, however, he began to gain weight rapidly and to develop pubic hair and penile enlargement. He was otherwise completely asymptomatic and had been very energetic and active, with good muscular strength. He had a good appetite without special preferences, although he ate a great deal of meat and potatoes. There was no special craving for salt or sugar. There were no voice changes, development of axillary hair, acne or other skin changes.

The past history revealed that he was born in breech presentation at term and weighed 6 pounds, 10 ounces. Weight gain and development were normal.

A review of the systems was negative except for an episode of "abscessed ears" and tonsillectomy eighteen months previously for frequent upper respiratory infections. He rarely wet the bed, and there were no other genitourinary symptoms.

Physical examination showed a well developed boy. The weight was 65½ pounds, and the height 46 inches. He seemed very plump, with prominent abdomen and hips. The neck and cheeks were fat. Examination of the head, neck and chest was negative. The heart was slightly enlarged to the left. The rate was normal, and there was a Grade II pulmonic systolic murmur. An electrocardiogram gave a normal tracing. The abdomen was plump and full, but no masses were palpable. There was definite, kinky pubic hair. The penis measured 7.6 cm. in length and 6.3 cm. in circumference. The testes were small and measured 1.9 cm. in cross section. The skin was clear, and there was no acne or unusual pigmentation. There was no axillary hair. Neurologic examination was negative.

The temperature was 99.2°F., the pulse 100, and the respirations 22. The blood pressure was 132 systolic, 96 diastolic.

The urine had a specific gravity of 1.022. The tests for sugar and bile were negative. There were rare red cells and white cells in the sediment. The blood hemoglobin was 14 gm., and the white-cell count 7700, with 78 per cent neutrophils, 14 per cent lymphocytes and 8 per cent monocytes. The eosinophil count was 112 cells per cubic millimeter. The serum chloride was 106 milliequiv., the sodium 140.4 milliequiv., the carbon dioxide 25.5 milliequiv. and the potassium 3.9 milliequiv. per liter. The nonprotein nitrogen was 17 mg., and the fasting blood sugar 86 mg. per 100 cc. (the blood sugar of a specimen taken two hours after breakfast was 97 mg.). A sample of sweat contained less chloride and more potassium per liter than normal. The urinary 11-17 oxycorticosteroid was 0.2 mg. per 24 hours. The 17-ketosteroids were 6.6 mg. per 24 hours.

X-ray films of the right hand and wrist indicated a bone age of seven years. Films of the skull failed to show any significant changes; the bones were of normal texture and density. The pituitary fossa was intact. Chest films showed clear lung fields. The heart was at the upper limit of normal size. The aorta was prominent. Anterior and posterior views of the abdomen showed normal appearance of the left kidney, spleen and liver. The right kidney was obscured by intestinal contents. There was no evidence of abdominal tumor.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FULLER ALBRIGHT*: This seems like a straightforward case, but one never knows in these exercises.

We know that this patient was producing too much androgen. The rapid somatic growth and the early development of the genitalia are evidence of this. Besides, the 17-ketosteroid excretion was 6.6 mg. per 24 hours, which is very high for a child of this age (normal value, 0 mg.). There are two tissues in the body that produce androgen: the reticular cells of the adrenal cortex and the Leydig cells of the testes. We therefore expect to find some disorder in one of these two tissues.

I will first discuss the reticular cells of the adrenal cortex. The first possibility I would consider is a tumor, benign or malignant, of the adrenal cortex. Everything in this case is compatible with such

*Physician, Massachusetts General Hospital.

a diagnosis. The rather short duration and rapid progress of the symptoms favor this diagnosis over some of the others, and this would be my first choice. Furthermore, by the law of averages I favor a malignant tumor. In my experience most of these tumors have been left-sided; so I would guess a left-sided tumor.

The second possibility I would consider is hyperplasia of the reticular cells of the adrenal cortex. This is a very interesting condition. It occurs mostly in females, and there is often a family history in the siblings. The typical story in females is usually as follows: together with certain characteristic changes in the external genitalia, the child is born with a large clitoris; she grows normally for the first one to eight years; she then develops axillary and pubic hair and grows rapidly, which suggests that androgen is being produced in excess somewhere in the body; finally, because of early epiphyseal union secondary to the excess of androgen, she stops growing at an early age. The net result is that her final height is about normal.

The reticular cells of the adrenal cortex have an interesting life history as worked out by the great Dr. Sam S. Blackman, Jr.[1] The fetal reticular zone is well developed and apparently functioning; in the first two weeks of postnatal life it retrogresses but leaves behind some cells that give origin to the postnatal reticular zone; these cells lie dormant until about puberty, when they again show signs of activity and produce reddish-brown granules.

The life history of the reticular zone in cases with hyperplasia of the reticular cells is modified. In the first place the fetal reticular zone is increased; in the second place the cells that give rise to the adult reticular zone lie dormant only one to eight years, rather than up to the usual time of puberty.

We are now in a position to interpret the clinical manifestations. The anatomic changes at birth are undoubtedly the result of increased androgen production by the hyperplastic fetal reticular zone; the failure of axillary and pubic hair to develop in the first few months is due to the latent period when the fetal reticular cells lie dormant; finally, the rapid growth of axillary and pubic hair and of the external genitalia, if it does occur, is evidence of the recrudescence of the reticular cells.

The reticular-cell hyperplasia not only is much less frequent in the male but also runs a somewhat different course. It is very apt to be associated with Addison's disease, because of the encroachment of the reticular cells on the other layers of the adrenal cortex.

Against the diagnosis of hyperplasia in this particular case are the failure of the genitalia to be enlarged at birth and the absence of any clinical or laboratory findings suggesting Addison's disease (for example, the serum electrolyte values and electrolyte values for sweat). On the other hand the onset of pubic hair and of rapid growth at six years of age is about the right time one would expect if this were the diagnosis. Furthermore, there must be cases in the male in which the activity of the fetal reticular zone is not sufficient to cause noticeable enlargement of the male genitalia. Finally, there must be male patients who do not have Addison's disease. Adrenocortical hyperplasia is my second choice.

I will now turn to possible disorders of the Leydig cells. First, a word about testicular function: the hypothalamus, by way of a neurohumeral pathway, stimulates the anterior pituitary body to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones, in turn, stimulate the testes, FSH leading to tubular development and LH controlling production of testosterone by the Leydig cell.

The first possibilty we might consider here as a cause of increase in androgen production is a tumor of the Leydig cells themselves. This is very rare. No such tumor was felt. In the only case I know of with this diagnosis, the 17-ketosteroid excretion was over 1000 mg. as compared with 6.6 mg. per 24 hours in this case. I think we can dismiss this diagnosis as possible but unlikely.

One might consider a tumor of the pituitary body giving off too much LH. Such a diagnosis would seem reasonable, but I never heard of a pituitary tumor that did this.

The next possibility to consider is a disturbance in the hypothalamus, releasing FSH and LH and stimulating all functions of the testes. One meets this condition in the so-called "pineal syndrome." It is initiated, not by the hormone of the pineal body, but by any tumor in the region of the pineal body. Against such a diagnosis in the case at hand is the failure of the testes to be enlarged. The size of the testes is dependent almost entirely on the size of the tubules, and in the pineal syndrome development of the tubular, as well as the Leydig cells, occurs. There are no findings to suggest an intracranial lesion, and I think we can dismiss this diagnosis.

Finally, one comes down to the possibility of a selective overproduction of LH without FSH. This might cause stimulation of Leydig cells without stimulation of tubules. I had never heard of such a syndrome until recently when Dr. Nathan Talbot mentioned it. I leave this for him to discuss. Such a diagnosis would seem to be compatible with the findings in this case, and I might put it down as a third choice.

It is now the vogue to divide adrenocortical hormones into three functional types, one for each layer of the gland. The innermost reticular layer is thought to produce the gluconeogenic, "sugar" or "S" hormone; the outermost glomerulosa layer is thought to produce the salt and water, sodium or "Na" hormone. It may be of interest to see what evidence there is for overproduction of each

one of these hormones by the tumor that I have diagnosed. We have already discussed the androgenic hormone. Against overproduction of the gluconeogenic hormone are the failure of the eosinophils to be decreased, the normal value for 11-17 corticosteroids and the rapid growth. In favor of some overproduction of the "Na" hormone is the hypertension and the low chloride and high potassium values in the sweat. It would seem, therefore, that this tumor was producing a large amount of androgenic hormone, a normal amount of the gluconeogenic hormone and a slightly increased amount of the "Na" hormone.

Dr. Nathan B. Talbot: Our preoperative diagnosis was the same as that just given by Dr. Albright. In the differential diagnosis the condition of greatest interest was a syndrome that we have now seen in a number of young boys. It is characterized by precocious masculinization, starting in early life. The testes are of normal size for age. The urinary 17-ketosteroid output is either normal or slightly elevated, and the urinary gonadotropin (FSH) assay is apt to be negative for 3 and 6 mouse units per 24 hours. Exploration of the adrenal glands of such patients fails to reveal either a tumor or bilateral hyperplasia. On the other hand, testicular biopsy reveals marked development of the interstitial cells of Leydig without more than minor evidences of testicular tubular development. It is believed that the precocity is due to a production of androgenic hormones by the Leydig cells and that these in turn have been precociously developed and activated by pituitary interstitial-cell-stimulating hormone (ICSH). It is further believed that the pituitary body has been activated to ICSH production by some sort of hypothalamic disturbance. Since most of these patients have shown no neurologic evidences of an intracranial lesion, it seems probable that the hypothalamic disturbance is of a functional nature rather than an organic, structural defect. Parenthetically, it may be added that the testicular interstitial cells occupy but a small volume; hence, it is possible for extensive interstitial-cell hyperplasia to occur without a clinically definite increase in gross testicular size. It is growth of spermatic tubules that accounts in the main for the increase in testicular size during adolescence.

So far as testicular size and masculine development were concerned, the patient under consideration corresponded to patients with the condition just described. On the other hand, he differed in the age at onset of precocity, which in his case was much too late for the above syndrome. He also differed in water and electrolyte status, for he had signs (questionable edema of the face, slight hypertension and cardiac enlargement) suggestive of a pathologic increase in the production of adrenocortical hormones of the type that cause sodium and water retention and potassium diuresis. To gain some objective information concerning the present patient's adrenocortical "Na-K" hormone status, Dr. William Locke applied a sweat electrolyte test on which he has been working recently. It might be interesting to hear the results of these studies.

Dr. William Locke: Methods for estimating the rate of secretion of the "Na-K" hormone are not so satisfactory as the methods for the other cortical hormones, as Dr. Albright and Dr. Talbot have said. In this case the hypertension may have indicated some overproduction of that hormone. The patient did not have hypochloremic alkalosis, which is sometimes associated with Cushing's syndrome and which has been attributed to an overproduction of the "Na-K" hormone in that condition. We have been studying variations in the electrolyte concentrations in sweat, with a view to using them as an index of "Na-K" hormone production. This subject was first studied by Dr. J. W. Conn,[2] who showed that desoxycorticosterone acetate has somewhat the same effect on sweat as it has on urine composition — that is, it reduces the concentration of chloride and sodium, and increases the concentration of potassium. In this case the sweat chloride was 10.0 milliequiv., and the potassium 13.2 milliequiv. per liter. Under the conditions of this test one would expect the chloride concentration in the sweat from a normal child to be perhaps three times what it was in this case and the potassium concentration to be approximately half what it was in this case. So we considered our findings to be suggestive evidence of an excessive production of the "Na-K" hormone.

Clinical Diagnosis

Carcinoma of adrenal cortex.

Dr. Albright's Diagnosis

Carcinoma of adrenal cortex.

Anatomical Diagnosis

Carcinoma of adrenal cortex.

Pathological Discussion

Dr. Oliver Cope: This patient had a tumor of the adrenal cortex. Why were the roentgenograms reported as showing no evidence of a tumor? The answer is that the tumor was small, not more than 3 cm. in its greatest diameter and scarcely large enough to cast a shadow. The roentgenograms were excellently clear, and a shadow was present on either side just above the kidney consistent with that cast by the adrenal gland. The shadow on the right was denser than that on the left. In making the incision we anticipated that if a tumor were present it would be on the right side. This proved to be the case.

It is a curious thing, as Dr. Albright has pointed out, that the overwhelming majority of the hyperfunctioning adrenocortical tumors we have encoun-

tered have been on the left side. Left-sidedness to me makes no sense so I am always equally suspicious of the right. This is the second right-sided tumor of our series. Left-sidedness is presumably a statistical fluke, and I suspect that with time and increased experience the left-sided predominance will also disappear.

Careful search was made at operation for evidence of malignant spread of the tumor. Grossly, the capsule of the tumor was unbroken. No invaded lymph nodes were encountered. The tumor was excised in toto.

The tumor was transected after removal at the operating table. On the gross examination I made a diagnosis of cancer because of the unevenness of consistence in one area and distortion of the stroma. These gross findings have been present in other malignant adrenocortical tumors and consistently absent in the small, apparently benign, tumors that have been resected from patients with Cushing's disease. My experience is too limited for me to be certain but I have a hunch that in such tumors the gross pathology is more reliable than the microscopical. I am therefore fearful of recurrence in spite of my negative search for lymph-node metastases.

Dr. Tracy B. Mallory: The tumor was a well encapsulated nodule of quite variable color with many bright-orange-yellow spots in it, indicating

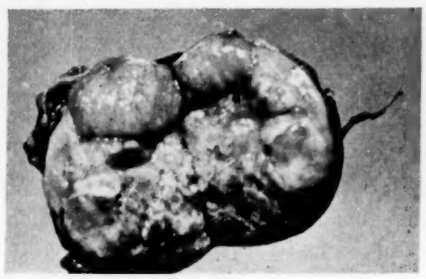

Figure 1.

that in portions of the tumor considerable lipoids were present (Fig. 1). The microscopical section showed a very variable picture (Fig. 2). Cells could be found that corresponded to all the various layers of the adrenal cortex. There were numerous lipoid-filled cells corresponding to the fascicular layer, and also many of the big rather homogeneous eosinophil cells that are found in the reticular layer. There was not a great deal of pigment in the cells in this case. The question comes up whether this tumor was benign or malignant. Encapsulation would be in favor of its being benign. In some parts of the tumor very atypical cells with giant multiple nuclei were found, which anywhere else in the body would certainly be evidence of a highly malignant tumor. Our experience in adrenal tumors has indicated that marked cellular atypicality of this type may be present in tumors that run a benign course. I think it very probable that if these slides were shown to a group of pathologists they would split fifty-fifty as to whether it was benign or malignant. My impression is that the outlook is relatively

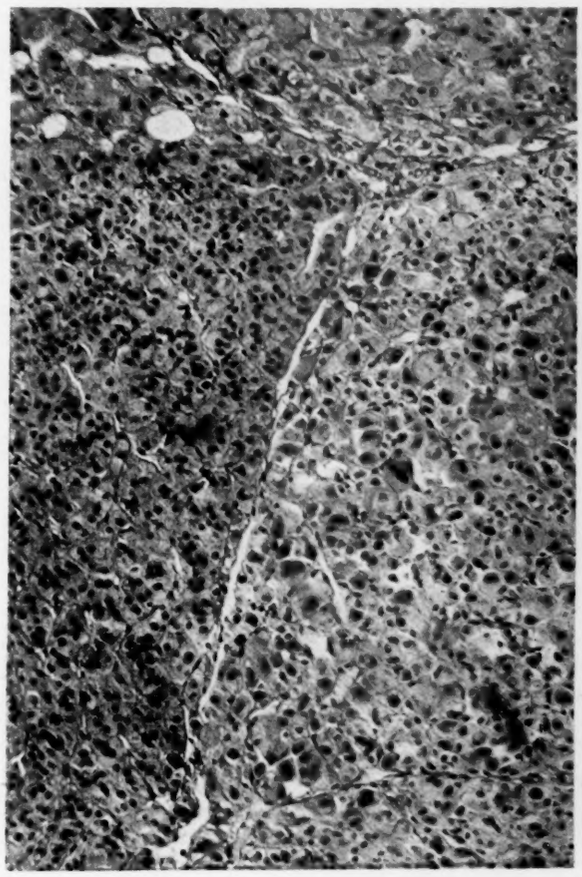

Figure 2.

favorable although we did call it carcinoma. That may perfectly well be an error.

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CASE 35482

Presentation of Case

A sixty-nine-year-old housewife was admitted to the hospital because of a "nervous breakdown."

She had suffered from a chronic nonproductive cough most of her life, and nine months before admission, coincident with an emotional strain, her cough became worse and her appetite failed.

A visit to her family doctor disclosed that she had lost weight and that her "blood was down to 70." She was given "iron pills," which, after a month, "raised her blood to 80." Six months before admission she noted the onset of weakness, increasing ease of fatigability, shortness of breath and increased anorexia. After two months she again consulted her doctor, who gave her ten injections of liver extract and prescribed liver pills, which she took religiously until the time of admission. No significant improvement in her symptoms followed this medication. One month before admission she first noted orthopnea, followed in two weeks by swelling of the ankles and legs. Constipation became troublesome at approximately the same time, and her stools became smaller in size. There was one brief episode of abdominal cramps, and it became necessary for her to take cathartics. Over the nine-month period there was progressive weight loss totaling 40 pounds. She had never experienced dysphagia, vomiting, hematemesis, melena, rectal bleeding or jaundice, and there had been no dysuria or gross hematuria.

At the age of twenty she suffered an attack of pneumonia complicated by "muscular and inflammatory rheumatism." The left breast was removed because of an "adenoma" thirty years previously. "Polyps" were removed intravaginally at thirty-five and sixty-nine years of age.

On physical examination the mucous membranes were generally pale. The tongue was red, with atrophy of the marginal papillae. The left breast had been removed by simple mastectomy. Tiny, firm, shotty lymph nodes were palpable in the left axilla. There was moderate kyphosis of the thoracic vertebra, and respiratory expansion was diminished. Breath sounds were distant, the percussion rate was hyperresonant, and scattered coarse rales were heard over both pulmonary bases. At 30° elevation the neck veins became distended and pulsating. The heart was enlarged to the left, and there was a Grade II precordial murmur. A++ pitting edema of the lower extremities extended upward to the knees. A large, hard, smooth mass was palpable in the right lower quadrant of the abdomen extending downward into the pelvis. One examiner believed that he could outline the lower border of the lesion by dipping the palpating fingers into the pelvis. The lesion was movable to palpation but unaffected by respiration. The liver and spleen could not be felt. On rectal examination there was palpable fullness in the right posterior quadrant, but a rectal shelf was not encountered. Vaginal examination was not completely satisfactory, and the uterine fundus was not outlined.

The temperature was 102°F., the pulse 100, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 1,160,000, with a hemoglobin of 3.5 gm., and a white-cell count of 9000, with a normal differential ratio but with 8 metamyelocytes and normal appearing platelets. The erythrocytes were hypochromic. No normoblasts were seen. Except for continued hypochromia subsequent blood smears were not remarkable. The hematocrit reading was 20 per cent. Reticulocyte counts were 0.6 per cent and 0.4 per cent respectively. A sternal-marrow aspiration was reported as not remarkable. Repeated urinalyses were consistently acid, with specific gravities between 1.008 and 1.013. Albumin varied from a trace to ++. The sediment contained 4 or 5 white blood cells per high-power field and 2 or 3 red blood cells per high-power field on one occasion. Occasional granular casts were seen. Twelve-hour urine concentration studies yielded a specific gravity of 1.012. The phenolsulfonephthalein excretion was 34 per cent in two hours. A urine culture grew a few colonies of colon bacilli. The total serum protein varied from 6.18 to 7.19 gm. per 100 cc., the albumin from 3.23 to 3.35 gm., and the globulin from 2.95 to 3.84 gm. Four successive nonprotein nitrogen determinations gave readings of 31, 68, 30 and 68 mg. per 100 cc. Successive prothrombin determinations were 52, 44, 57, 48 and 70 per cent of normal. A van den Bergh reaction was less than 0.4 mg. per 100 cc. on direct and indirect tests on one occasion, and 0.2 mg. direct, 0.4 mg. indirect, on another. The alkaline phosphatase varied between 20.1 and 16.9 units per 100 cc. The cephalin-flocculation test was + at twenty-four and ++ at forty-eight hours. Urinary urobilinogen examinations were 0.25 and 0.29 Ehrlich units respectively. Bromsulfalein excretion studies showed 14.2 per cent retention of the dye in forty-five minutes.

A cytologic examination of smeared vaginal secretions was negative. An electrocardiogram was within normal limits. A barium enema showed lateral and upward displacement of the cecum, ascending colon and proximal transverse colon by a large, smooth mass lying in the right lower quadrant. The deformity was that of a pressure defect, with no evidence of involvement of the wall of the colon.

A chest x-ray examination revealed increased linear markings throughout both lung fields. The heart was slightly enlarged in the region of the left ventricle. The aorta was moderately tortuous and calcified in the region of the arch.

Films of the skull and lumbar spine were negative for evidence of metastases.

In an intravenous pyelogram there was an insufficient amount of opaque material on either side to warrant adequate visualization of the urinary passages. The right kidney could not be traced. The left seemed lower than usual but within normal limits. There was an impression of a rounded, soft-tissue mass occupying the right side of the

pelvis (Fig. 1). A residue of barium was caught in a sigmoid diverticulum and in the appendix.

The patient was placed on complete bed rest, digitalized and given Hykinone, elixir of ferrous sulfate, 10 per cent hydrochloric acid and liberal supplements of vitamins with a salt-restricted diet. The temperature fluctuated between 100 and 101°F. for the first seven days and then fell to normal (the weather was exceedingly warm during this period). After three days the pulse fell to normal limits.

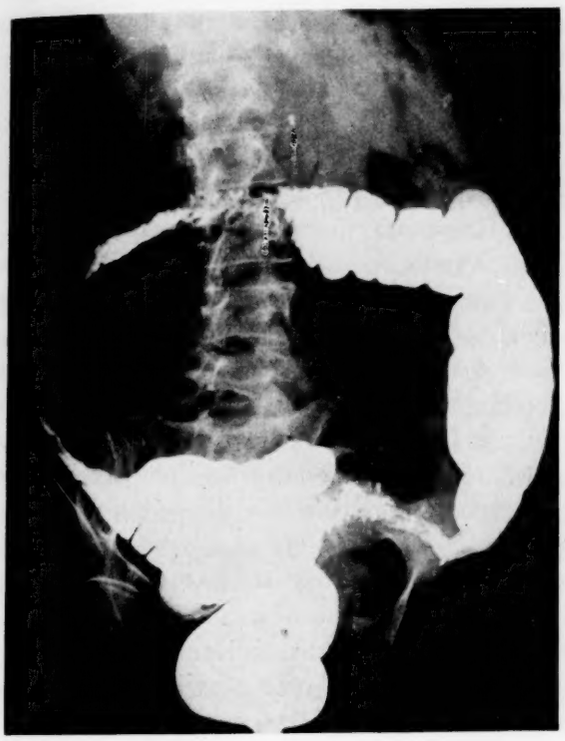

FIGURE 1.

Over the first three days she received 0.4 cc. of Mercupurin in divided doses, with a 6-pound weight loss and slight relief of orthopnea. A total of 4000 cc. of whole blood and the packed erythrocytes from 1500 cc. were given during the first fifteen days. One transfusion was followed immediately by a febrile reaction, the temperature reaching 102° F. This subsided promptly without jaundice or hemoglobinuria. There was a steady rise in hemoglobin from 3.5 to 9.0 gm. following the first seven transfusions. Three subsequent 500-cc. transfusions in the ensuing four days failed to produce further elevation. A hematologic consultant was unable to determine the cause of the anemia, which he classified as normocytic and slightly hypochromic. As the blood count rose the cardiac status improved. There was subsidence of peripheral edema and great diminution in the pulmonary rales. No cause for the wide variation in the blood nonprotein nitrogen was established. On the twenty-first hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. W. PHILIP GIDDINGS*: This history concerns an elderly woman with symptoms and signs suggesting disorder of nearly all the major body systems. Perhaps some of these are interrelated, and we can reduce the problem to simpler terms.

It is obvious that she was severely anemic, and the evidence all indicates a so-called secondary anemia. One immediately suspects chronic blood loss, but we are given no apparent source of bleeding. It is both regrettable and amazing that no stool examinations for occult blood are recorded.

After her anemia, the next apparent difficulty is that she was in cardiac failure. The suggestion by history of possible rheumatic fever at the age of twenty is not borne out by the electrocardiogram; at least she did not have evidence of rheumatic heart disease, nor was the murmur described suggestive of a specific lesion. With diuretics and correction of her anemia, the cardiac status improved, and it is justifiable to conclude that her heart failure was largely if not wholly due to the anemia. At least that is my conclusion.

The next striking fact is that her renal function was impaired: she showed albumin, casts and red cells in the urine. The specific gravity did not rise above 1.013, phenolsulfonephthalein excretion was about half of normal, and she did not concentrate intravenous dye sufficiently for x-ray visualization of the upper urinary tract. All this bespeaks a diffuse renal lesion, which I take to have been independent of her other difficulties. I suppose she had a chronic glomerular nephritis, and shall ascribe the albumin and nonprotein nitrogen levels to this.

Let us now consider her liver. Here again we find evidence of functional impairment. The albumin-globulin ratio was decreased; bromsulfalein retention, alkaline phosphatase and prothrombin time were all elevated, though none of them to a very marked degree. Cephalin flocculation was ++ at forty-eight hours. Urinary urobilinogen and van den Bergh values were normal. In my limited knowledge of such matters, I should conclude that although a diligent search was made for evidence that some sort of biliary-tract disease underlay the clinical picture, the findings did not suggest a major hepatic disorder. I do not know whether or not her severe anemia, nephritis, cardiac failure and probable malnutrition could produce this picture in the liver, but I suspect that they might.

I should mention in passing her chronic cough. I see no cause for this in the history, physical examination or x-ray findings, except that its increased severity recently was due to pulmonary edema.

*Assistant in surgery, Massachusetts General Hospital.

We shall pass it over — possibly unwisely — as an unexplained and irrelevant matter.

We now come to the crux of the story, the mass in the right lower quadrant of the abdomen. This was probably a surgical lesion and is the reason for my having been assigned this case. I must confess, with apologies to my medical colleagues, that now for the first time I feel on familiar ground.

The tumor was large, smooth and hard. We immediately think of the cecum, kidney, liver, gall bladder and ovary as possible origins of such a mass. That it was not inflammatory is evidenced by its mobility, implied lack of tenderness, normal leukocyte count and absence of sustained fever. Nonmalignant hard tumors are unusual unless calcified, which is the reason that I suspect this was cancer.

Was it ovarian? One observer demonstrated it to be out of the pelvis, and it was not definitely palpable on vaginal examination. I do not think it was in the ovary. The physical examination and x-ray films do not agree with the behavior of hepatic or cholecystic tumors, and I believe we can rule out the liver and gall bladder. Nor could it have been kidney: a movable renal mass would have descended with respiration, and this did not.

In a patient with anemia of this degree and a mass at the right lower quadrant, one would like to know the guaiac reaction on the stool.

Dr. Tracy B. Mallory: Three specimens were examined: one was negative; one was +; and one was + or —.

Dr. Giddings: I might say, it is rather surprising that a retrograde pyelogram was not done, since the mass in the right lower quadrant was sufficient in size to displace the major viscera. One would think the surgeon would want to know the precise relation of the ureter to the mass, but I gather that the investigation there was not done. I would also question once and for all whether this could have been a renal tumor. I do not think it was.

That leaves us with the cecum, unless we consider such rarities as mesenteric tumors. This would be a good time to see the x-ray films.

Dr. Stanley M. Wyman: The chest film taken in the supine position is that of an elderly woman with an enlarged heart, apparently chiefly left ventricular, with a tortuous arteriosclerotic aorta. The lung fields, themselves, reveal no definite active localized disease, but there does appear to be considerable emphysema, as shown by increased anteroposterior diameter of the chest. The films from the barium enema demonstrate quite conclusively a large mass lying in the right lower abdomen over the sacrum, lumbar spine and iliac crest (Fig. 1). This displaces the right colon as described. The pressure is chiefly on the ascending colon, and to a lesser degree on the cecum and on the hepatic flexure. There is no evidence of intrinsic involvement although the mass may be adherent to the colon. The cecum itself is quite well seen in this film and lies lower and more medially than usual, in keeping with the pressure from the mass. There is a definite area of dense calcification seen in the right midabdomen, better seen on several other films. This does appear to be important and is not consistent with a calcified lymph node.

Dr. Giddings: Could it be a vessel?

Dr. Wyman: I do not believe so. The patient does have tortuous arteriosclerotic vessels in the pelvis, and probably higher up than I can demonstrate in the aorta. There is some calcification to the left of the spine — possibly, in the splenic artery. The mass is better seen in films of the attempted pyelogram. It lies below the right kidney. The kidney on the right is not outlined, but what seems to be its lower pole is not grossly remarkable. The left kidney is definitely small, measuring perhaps a quarter of the usual size. The calcification is present in all these films, and it occupies essentially the same position. To me, that is one of the more interesting features of these films.

Dr. Alfred E. Kranes: How about the visualized bones? Do they show any changes of metastatic involvement?

Dr. Wyman: They seem diffusely osteoporotic, in keeping with the patient's age. I do not see any gross metastases, but we know that with osteoporosis we can miss extensive metastases with great facility.

Dr. Giddings: That does not make me feel any better. I am at a loss to explain the calcification here. It was not mentioned before.

Of course, the diagnosis that immediately suggested itself to me was carcinoma of the cecum. This is a classically insidious tumor that frequently grows to large size before its detection. One of its most characteristic features is an accompanying severe anemia of the hypochromic variety. As Alvarez and others have pointed out, the cecum

is one of the first places to look in searching for the cause of an obscure secondary anemia. (The next is the stomach.) So far as I know, the precise reason for the anemia is not known.

In spite of the x-ray findings, I am constrained to make a diagnosis of carcinoma of the cecum. It fits the picture too well for me to consider any other. An obvious diagnosis to consider is metastasis to the peritoneal cavity from a carcinoma of the breast removed thirty years previously. I see no way to support such a diagnosis. The question arises whether or not her liver difficulties could have been due to metastatic disease. Although cancer of the right colon typically metastasizes late, this was a large tumor and could well have spread through the portal system. I am certain that we cannot answer this question definitely, but I should not be surprised to learn that she had liver metastases.

I do not know whether an intramural tumor of the wall of the bowel at this level, such as a neurofibroma, would give this picture. It does not look at all like a lipoma. Neurofibrosarcoma would produce the same effect in the way of anemia as the classic carcinoma of the bowel, but I do not know whether or not it would still leave the mucosal pattern intact. I am going to guess that she had a primary neoplasm of the right colon of some sort.

Dr. Wyman: From the x-ray standpoint I do not think it is tenable to place the primary tumor, especially carcinoma, in the right colon. I wonder if Dr. Giddings would consider a papillary cystadenoma or cystadenocarcinoma of the ovary?

Dr. Giddings: It is conceivable that the mass is a little lower in the film than I judged it to be from the physical examination as recorded. Ovarian tumors are usually capable of being bimanually palpable.

Dr. Wyman: We have seen them as high as and higher than this in many cases.

Dr. Daniel S. Ellis: Are the x-ray findings consistent with a dermoid cyst?

Dr. Wyman: It should be of less density because it contains fat. This seems to be of increased density.

Clinical Diagnosis

Carcinoma of ovary.

Dr. Giddings's Diagnoses

Tumor of cecum.
Secondary anemia.
Cardiac failure.
Chronic glomerular nephritis.
Metastases to liver?

Anatomical Diagnosis

Renal-cell carcinoma of right kidney.

Pathological Discussion

Dr. Somers Sturgis: This woman looked older than her stated age, and she was moribund on admission. When the service first saw her she was desperately sick, and it was very questionable in their minds whether they could ever get her in shape for surgery. The gynecologic service favored an ovarian lesion and rather suspected that she had a diffuse carcinomatosis to account for the anemia and lack of much guaiac in the stool. It was on that basis and with that diagnosis in mind that she was operated on.

The laparotomy was done, and a large, smooth, nonadherent, encapsulated tumor was found retroperitoneally, lying behind the ascending colon. The pelvis was normal. The uterus was small, and both ovaries were atrophic. It was obvious that this was a renal neoplasm. It was dissected off without difficulty from the ascending colon.

Dr. Mallory: The resected specimen was an enlarged kidney, enlargement being due to a characteristic renal-cell carcinoma, which had not invaded the renal pelvis. This explains why there had not been, at any time, hematuria. The tumor had not extended into the renal vein as they so often do. The patient made a good operative recovery and left the hospital comparatively well.

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OLIVER WENDELL HOLMES AND BIOSTATISTICS

A CENTURY ago when a patient died from puerperal infection, the physician (and doubtless the patient) was considered merely unlucky. Holmes, however, was not content to stomach this kind of ill luck. He gathered the facts, quantitated them and proved statistically that the doctor was more than unlucky. He was a "pestilence carrier (who) must look to God for pardon for man will never forgive him."

Holmes "had the chances calculated that a given practitioner shall have sixteen fatal cases in a month." By comparing this "unlucky" series of sixteen births with the total number of births in the community not complicated by infection, he found that "there was not one chance in a million million millions that such a series should be noted" as a purely fortuitous phenomenon.

During the intervening hundred years, while the controversial aspects of puerperal sepsis were being settled, the mathematicians have been busy, first with whittled pencils and then with slide rules and calculating machines perfecting modern biostatistics. It is not necessary to wait for odds of a billion billion to one in order to demonstrate the significance of an observation, and the textbook on biostatistics is today part of the research-minded physician's vade mecum, whether he likes it or no.

The "or no" reaction, however, is so common as to be almost instinctive among the majority of physicians, who have no occasion to use the binomial theorem when computing doses of sulfadiazine or cutting for the stone. To those who enjoy a kind of statisticophobia, who nevertheless are compelled by the inner spirit of curiosity and research to study a series of operations, autopsies, blood counts, x-ray examinations or whatnot in order to find the solution to some challenging medical problem, a recent progress report by Luykx* will be found worthy of thoughtful reading. The purpose of Luykx's contribution is to give "the reader of medical and scientific literature, the medical 'common man'" an appreciation of the need for, and the purposes of, proper presentation and analysis. "The student of medicine must have some knowledge of technics of handling quantitative data (1) in order to understand a correct presentation and (2) in order to form a judgment. . .as to whether a given exposition or analysis is adequate or not."

Although electric calculators have made Einsteins of office secretaries, Luykx makes it abundantly clear that there is more to a formula than grinding it through the machine. Practicing physicians will be cheered by the statement:

> The technic of calculating the mean and standard deviation will not be discussed here. This is a matter of the proper use of a calculating machine or a slide rule. Much more important is a correct understanding of the meaning of these parameters.

*Luykx, H. M. C. Progress without statistics. Council on Pharmacy and Chemistry. *J. A. M. A.* **141**:195-201, 1949.

The Autocrat of the Breakfast Table would also have enjoyed reading Luykx's lucid exposition of his subject, "Progress without Statistics." In the judgment of the *Journal* his analysis is adequate.

INDUSTRIAL MEDICINE — A NEW PROGRAM

A BLUEPRINT for the expansion and improvement of industrial medicine in Massachusetts will be offered on December 14 at 2:00 p.m. at the Hotel Statler, in Boston, by the Committee on Industrial Health of the Massachusetts Medical Society. This venture is a logical outgrowth of the Massachusetts Health Conference in February, on which occasion it became evident that a fresh outlook and a renewed effort were needed. The interest was present, but the initiative seemed then to be lacking.

Since that meeting the Committee on Industrial Health has been reorganized with new and enthusiastic membership, and a section on industrial health has been established in the Society. It is under such auspices that the program of December 14, published elsewhere in this issue of the *Journal*, will be presented.

Massachusetts is a highly industrialized state in which many physicians who devote their full time to the medicine of industry have done excellent work, and in which many others, engaged in part-time activities, have discharged their functions with varying degrees of competence and effectiveness.

The actual practice of industrial medicine is, fortunately, an area in which there can be little real conflict between labor and management. Management, when properly informed, is as eager to improve existing programs or institute new ones for the health and safety of workers as labor is to cooperate in attaining the same high objectives. The physician, as the working agent, is equally respected by both sides.

In this effort to bring together representatives from management, labor, industrial nursing and industrial medicine to discuss common problems and work out effective solutions, the interest of all physicians is sought.

INFECTIONS WITH THE "COXSACKIE VIRUS"

THE discovery by Dalldorf and Sickles[1, 2] of a new virus from human cases resembling poliomyelitis and the subsequent isolation of this virus by Melnick, Shaw and Curnen[3] from cases that were diagnosed as nonparalytic poliomyelitis, aseptic meningitis or fever of unknown origin were recently reviewed in these columns.[4] The latter workers found the new virus to be widespread in this country during the summer of 1948. Certain new and significant observations have been added by the original discoverers[5, 6] and deserve mention in view of the interest stimulated by their work and because of the extensive epidemics of poliomyelitis that have occurred in and around Boston during the past summer.

The new virus was originally isolated by the Albany workers from 2 young boys who suffered from what was believed to be paralytic poliomyelitis during August, 1947. The authors usually referred to it as the "suckling mouse virus" because it was originally isolated by intracerebral inoculation of mice three to seven days old. They have now chosen to call it the "Coxsackie virus" after the village in upstate New York where the first human cases were recognized.[6]

Dalldorf[5] later isolated his virus from 5 out of 21 fecal specimens collected during a rather large epidemic of poliomyelitis that occurred in 1947 in Wilmington, Delaware. This epidemic was noteworthy because other investigators had failed to isolate the classic poliomyelitis virus from the patients, so that the new virus was considered as probably causally related to some of these cases. Some of the clinicians and epidemiologists who investigated this outbreak considered the disease to be atypical in two respects: the unusually large number of multiple cases in families and the transient nature of the paralysis in many patients.

Additional studies were carried out by the Albany workers during 1948 in the course of which they isolated the new virus from 10 out of about 130 specimens collected from "poliomyelitis" patients in upstate New York.[5] These isolations were from widely scattered outbreaks and from isolated cases,

and the studies show that the agent was widely disseminated in New York State during that summer. Furthermore, at least one antigenically distinct strain and possibly others identified differ in the nature of the disease they produce in mice.

The earlier strains were incapable of infecting monkeys and had the unique property of causing disease only in very young mice and hamsters although this may later be modified experimentally. In mice they caused lesions of the muscles rather than of the central nervous system. They were thus distinct from the classic monkey-pathogenic poliomyelitis virus, which produces central-nervous-system lesions in monkeys and shows no antigenic relation to the new virus. Certain of the new strains, however, appear to produce lesions in both the muscles and the central nervous system. Thus far, even these new strains have failed to cause lesions that resemble those of poliomyelitis.

Pathological studies of patients have, to date, been quite limited because the only fatal cases have apparently been caused by classic strains of poliomyelitis virus. This leads one to suspect that the new agent is less malignant for human beings than the monkey-pathogenic strains. Studies in the experimental disease have also indicated that the serologic diagnosis of infections with the new agent may be quite difficult.

In the mice the outstanding lesion has been the destruction of muscle that becomes a rich source of virus. The muscle degeneration suggested the possibility that studies of creatine and potassium balance might be used as a diagnostic aid. Infected mice were found to develop quite rapidly a marked creatinuria coincident with a loss of muscle potassium and creatinine.[6] It was therefore suggested that similar studies might be useful in human cases.[5]

In discussing these findings, Gifford and Dalldorf[6] cite reports from the literature of creatinuria following paralytic poliomyelitis. The muscle findings in reported cases of poliomyelitis, however, have been variable and obviously require re-examination in the light of the more recent findings in experimental infections with the Coxsackie virus. Furthermore, the reports of cases of poliomyelitis in which muscle groups that apparently were totally paralyzed have rapidly and completely recovered their function likewise require re-evaluation. It is hoped that future observers will have available more extensive studies of muscles from cases of suspected poliomyelitis, with and without paralysis. It is necessary to determine whether the muscle lesions caused by the classic poliomyelitis virus and by the new viruses have distinctive clinical and histologic features and also what the pathogenic potentialities of these tissues may be. This is particularly important in view of the finding of central-nervous-system lesions produced by some of the new strains.

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HEAT VERSUS VIGOR

THE importance of temperature as perhaps the leading environmental factor determining the success of man's attempts at life on this planet is stressed by Mills,* writing for *Science*. His analytic essay, emanating from the Laboratory for Experimental Medicine of the University of Cincinnati, suggests that it's not so much the humidity that counts as it is the heat — although the humidity also plays its part.

If the animal body is considered somewhat in the light of an internal combustion engine, the working efficiency of men, horses and dogs ranges between 20 and 25 per cent, and even this degree of efficiency depends on the rapid dissipation of its waste heat. Diesel did better, having achieved a working efficiency of 40 per cent for his well known engine.

In view of such a summer as New England and other parts of the world have recently experienced, it is easy to agree with Mills that the lowered com-

*Mills, C. A. Temperature dominance over human life. *Science* **110**: 267-271, 1949.

bustion rate subsequent to weeks of difficulty in dissipating waste heat leads to a decline in available energy for thought and action and even for such functions as growth, rate of development and resistance to infection.

Contrary to the current belief that human development in tropical climes is early and particularly luscious, Mills points out that children raised in the regions of oppressive heat "grow slowly, mature late, and are, in the main, of inferior stature." The Island of Bali may produce gorgeous specimens of humanity; the inhabitants of Equatorial Africa are forced to admit that it can't happen there.

Various interesting biologic tests uphold the main contention. The human brain has been shown to function best in an environmental temperature from 38 to 40°F., and college students, the world's future braintrusters, show better aptitude tests in the winter than in the summer. Experiments with white rats have borne out the observations made on college students; those kept at a temperature of 55°F. have better memories and possess more *joie de vivre* than other specimens maintained in temperatures of 75 and 90°F.

Both the rate of human conception and the caliber of its products are apparently also determined by the season. Employing the accepted American standard of success, Mills carries his *reductio* to the point of *absurdum* by noting that eleven of our presidents were conceived in the first quarter of the year, ten in the second, only four in the hot third and seven in the fourth. The thirty-second occupant of the executive mansion, according to Mills, is the only one to have been conceived in August!

Human capacity for achievement, it appears, follows the periodic advances and recessions of the polar icecaps. The glory of classical antiquity reached its full development in a cold millennium and was succeeded by the warmth of the Dark Ages "when cereal grain could be ripened in Iceland and grapes in England." The next advance of the cold front over central Europe was responsible for the Renaissance, but a recession has again set in, and a semitropical warmth is beginning to sap the vitality of the dwellers in what was so recently the temperate zone. Meanwhile Russia, released from the icy bondage of countless centuries, is already benefiting from invigorating optimal temperatures. This new environmental stimulus should add considerable weight to her claims that in Russia the steam engine, the telephone, the automobile, the airplane and no doubt the atom bomb and the cotton gin were actually invented.

Dr. Brown, of Manchester, N. H., now in California, has found good picking at the gold mines.—Scarpa's Acoustic Oil, that made the deaf hear, at two dollars a bottle, is a very good substitute, excepting price, for neat's foot oil, on boots and shoes.

Boston M. & S. J., *November 28, 1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

HARRIS — Lorne W. Harris, M.D., formerly of Saugus, died on November 9. He was in his seventy-second year.

Dr. Harris received his degree from Jefferson Medical College of Philadelphia in 1908.

His widow and a daughter survive.

CONFERENCE ON INDUSTRIAL MEDICINE

The following program will be presented by the Committee on Industrial Health of the Massachusetts Medical Society in the Salle Moderne of the Hotel Statler, Boston, on Wednesday, December 14, at 2 p.m.

Opening Remarks. Henry C. Marble, M.D., chairman, Committee on Industrial Health.

"The Physician in Industrial Medicine." Robert B. O'Connor, M.D., medical director, New England Division, Liberty Mutual Insurance Company, Loss Prevention Department.

"Recent Advances in Industrial Medicine." Albert O. Seeler, M.D., assistant professor of industrial medicine, Harvard University School of Public Health; and Harriet L. Hardy, M.D., associate physician in charge of Occupational Medical Services, Medical Department, Massachusetts Institute of Technology.

Clinical Demonstration.

"Effective Small Plant Medical Program." Mr. William H. Seymour, vice-president, Liberty Mutual Insurance Company.

"Heart Disease and Industry." Howard Sprague, M.D., president-elect, American Heart Association.

Social Hour. 5 p.m.

Dinner Meeting. 6 p.m. Chairman, Arthur W. Allen, M.D., president, Massachusetts Medical Society.

Remarks by Mr. Andrew B. Holmstrom, vice-president and general manager, Norton Company, Worcester, Massachusetts; Mr. Albert G. Clifton, legislative agent, Congress of Industrial Organizations; and Mr. Kenneth J. Kelley, secretary-treasurer and legislative agent, Massachusetts Federation of Labor. "Rehabilitation of the Chest Patient." Dwight E. Harken, M.D., assistant clinical professor of surgery, Harvard Medical School, visiting thoracic surgeon, Boston City Hospital, and senior associate in thoracic surgery, Peter Bent Brigham Hospital.

CORRESPONDENCE

A PHYSICIAN DISAGREES

To the Editor: Fair-minded physicians who are members of the American Medical Association must feel ashamed of the official statement put out by the Board of Trustees of the Association in the October 15 issue of the *Journal*. In this statement the Trustees accuse the Department of Justice of the United States of waging a campaign to discredit American medicine and terrorize physicians into abandoning their opposition to compulsory health insurance. A careful perusal of the complete statement fails to show any concrete evidence to support this claim. A series of assumptions apparently forms the basis for this attack upon the integrity of the Justice Department of the United States.

In view of the past history of the American Medical Association and the evidence of persisting activities on the part of various groups in organized medicine, in violation of existing laws, to interfere with the development of plans to improve the delivery of medical care it seems that the Trustees are not in a very satisfactory position to try to besmirch the activities of the Department of Justice.

Actually, in 1938 the American Medical Association was convicted for breaking certain laws in the celebrated case of the Group Health Service in the District of Columbia, and this conviction was eventually upheld by the Supreme Court of The United States. In this instance it was the American Medical Association that was trying to discredit a group of physicians and to terrorize physicians from developing a plan to deliver medical care. Since then the Department of Justice has been receiving complaints from physicians and lay groups that similar tactics are being employed by organized medicine throughout the country. Investigation has provided enough evidence of disregard of the law by organized medicine to make the Department of Justice decide to bring suit in two instances. It seems only fitting in view of these facts that the Department should investigate further the numerous complaints that are made to it. To claim without evidence that such actions are aimed at terrorizing physicians rather than to compel them to obey the law seems quite unworthy of men honored by the medical profession to hold the high office of Trustees of the American Medical Association. I believe the national medical society should urge individual physicians and organized groups of physicians to obey the laws as they exist.

If any group does not believe in the existing laws it is fitting that attempts should be made through authorized methods to change them. The profession and the public should realize that there are thousands of reputable physicians who believe in the development of a national health program to be financed in part by compulsory health insurance such as President Truman favors.

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NOTE: Further perusal of the statement issued by the Board of Trustees discloses the following paragraphs, relating to the alleged threatening of medical societies by Administration leaders: "On February 28, 1949, for example, one of the National press associations carried a dispatch from Washington quoting Government officials as stating that anti-trust actions would be started against 'several' medical societies *soon after the Compulsory Health Insurance drive was started in Congress* [*italics ours*]." — ED.

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Food Poisoning. By G. M. Dack, Ph.D., M.D., professor of bacteriology and director, Food Research Institute, University of Chicago School of Medicine. Revised edition. 8°, cloth, 184 pp., with 13 tables. Chicago: University of Chicago Press, 1949. $3.75.

This second edition of a special work has been revised, and the subject brought up to date. The various chapters include chemical poisoning in food, poisonous plants and animals, botulism, staphylococcal food poisoning, salmonella, alpha-type streptococci (*Streptococcus faecalis*) in relation to food poisoning, significance of other bacteria and infections to be differentiated from food poisoning. Lists of references are appended to the chapters. There are indexes of authors and subjects. The small book is well published and should be in all medical libraries.

Public Health in the World Today. Edited by James S. Simmons, dean, Harvard School of Public Health; assistant editor, Irene M. Kinsey. With a foreword by James B. Conant, president of Harvard University. 8°, cloth, 332 pp. Cambridge, Massachusetts: Harvard University Press, 1949. $5.00.

The papers presented in this volume were delivered during 1947–1948 at the public-health forums, conducted by the Harvard School of Public Health. Twenty-three eminent persons in their particular fields participated in the forums. The material is divided into various aspects of public health as follows: the profession of public health; public health in the United States today; public-health programs and problems abroad; and public health in a new era. The volume is excellently published but is marred by the lack of an index. It should be in all collections on the subject.

Natural Products Related to Phenanthrene. By Louis F. Fieser and Mary Fieser, Department of Chemistry, Harvard University. Third edition of the monograph previously entitled *Chemistry of Natural Products Related to Phenanthrene*, by L. F. Fieser. 8°, cloth, 704 pp., illustrated. New York: Reinhold Publishing Corporation, 1949. $10.00. (American Chemical Society Monograph No. 70.)

The authors have revised this standard reference book to bring it up to date. The first and second editions were published in 1936 and 1937. Despite its formidable title, the work is definitely of medical interest. Some of the chapters discuss the quinone and opium alkaloids, sterols and bile acids, sex hormones, adrenal cortical hormones, steroid metabolism and cardiac active principles. The pertinent literature is cited in footnotes on the appropriate pages. There are comprehensive indexes of authors and subjects. The printing is well done with a good type on light-weight paper, producing a volume light in weight for its size and yet conserving space. The volume is a good example of publishing in which some consideration is given the prospective reader. The book should be in all medical, physiologic and chemical libraries and in commercial laboratories.

Histology and Histopathology of the Eye and Its Adnexa. By I. G. Sommers, M.D., assistant professor (ophthalmology), College of Medical Evangelists, and medical office (E.E.N.T.), United States Public Health Service, Los Angeles, California. 8°, cloth, 784 pp., with 69 illustrations. New York: Grune and Stratton, 1949. $12.00.

This new book is based on the lecture courses given by the author over many years to his students. The text is divided into three parts: normal histology, embryology and senescence; general pathology (in relation to the eye); and histopathology of the eye. Under the heading "Reading of Source Material," extensive lists of short pertinent excerpts

from fundamental contributions of various authors are appended to the various chapters, which also include extensive bibliographies. For the literature previous to 1920, the reader is referred to Vol. 11 of the *Handbuch der speziellen pathologischen Anatomie und Histologie, Auge*, Berlin, 1928–1937. The book is well published but sparsely illustrated for its type. It should be in the reference collections of all medical libraries and available to ophthalmologists.

Fundamentals of Internal Medicine. By Wallace M. Yater, M.D., M.S. (in Med.), director, Yater Clinic, Washington, D.C. Third edition. 8°, cloth, 1451 pp., with 315 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1949. $12.00.

This new edition of a standard treatise has been thoroughly revised and brought up to date. Eighteen collaborators have written certain chapters of the text. A new and enlarged article on electrocardiography has been included. Sections on chemotherapy and therapy with antibiotics and on inhalation therapy have been added. The drug dosage has been given in the metric system and the old apothecary system discarded. A comprehensive index concludes the text. The book is well published and should be in all medical libraries and available to the practicing physician.

International Digest of Health Legislation. Vol. I, No I, 1948. 8°, paper, 144 pp. Geneva, Switzerland: World Health Organization, 1948.

This new periodical succeeds the first section of the *Bulletin mensuel de l'Office International d'Hygiène Publique*, which ceased publication in December, 1946. It comprises the orders, decrees and regulations for the governments in the World Health Organization. It is published in two languages, English and French, and issued as separate or bound numbers. This is the English edition in bound form.

Diseases of the Liver, Gallbladder and Bile Ducts. By S. S. Lichtman, M.D., assistant professor of clinical medicine, Cornell University Medical College, assistant attending physician, New York Hospital, adjunct physician, Mt. Sinai Hospital, and assistant in postgraduate medical instruction, University Extension, Columbia University. Second edition. 8°, cloth, 1135 pp., with 147 illustrations and 2 color plates. Philadelphia: Lea and Febiger, 1949. $18.00.

The text of this second edition of a standard work has been completely revised. The chapter on infectious hepatitis has been completely rewritten. Large bibliographies are appended to the various chapters. There is a comprehensive index. The book is well published and is recommended for all medical libraries and to all persons interested in the liver and its diseases.

Tumors of Bone. By Charles F. Geschickter, M.D., professor of pathology, Georgetown University School of Medicine, consultant in pathology, United States Naval Medical School, consultant in pathology, Mt. Alto Veterans' Administration Hospital, and pathologist-in-chief, Gallinger Municipal Hospital, Washington, D.C.; and Murray M. Copeland, M.D., professor of oncology, Georgetown University School of Medicine, consultant in surgery, Gallinger Municipal Hospital, Washington, and special consultant, Federal Security Agency, Public Health Service, Cancer Control Branch, Washington. Third edition. 4°, cloth, 810 pp., with 642 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $17.50.

The previous editions of this standard treatise were published in 1931 and 1936. The third edition has been thoroughly revised, and the subject brought up to date. Chapters on fibrous dysplasia, osteoid osteoma, tumors of the spine, endocrine changes in bone and rare diseases of bone have been added. The chapters on embryology, chondroblastomas, and treatment of bone sarcoma have been entirely rewritten. The tabulations of bone tumors, on which the book is based, have been extended to include more than 500 additional cases. The illustrations have been revised by the addition of more than a hundred new ones and the deletion of a large number of the old ones, with the object of presenting the best possible reproductions of representative roentgenograms, gross specimens and photomicrographs. Lists of selected references are appended to the various chapters. There is a good index. The publishing is well done, and the illustrations are excellent. The book, although justifiably expensive, should be in all medical libraries, and available to pathologists, orthopedists and surgeons.

The Temporal Bone and the Ear. By Theodore H. Bast, Ph.D., professor of anatomy, University of Wisconsin Medical School, and Barry J. Anson, Ph.D., professor of anatomy, Northwestern University Medical School. 8°, cloth, 478 pp., with 165 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $12.00.

This monograph presents a comprehensive study of the development and the adult anatomy of the ear and the temporal bone. Concerning the pathology of the ear, only such information is given as relates to development. The text has been organized on a developmental basis, beginning with the otic labyrinth, after the first chapter on the general anatomy of the temporal bone and the ear. The following chapters discuss the periotic labyrinth, the otic capsule, histologic variations and pathologic processes, bone dystrophies, the origin and development of the middle ear and related air spaces, and the auditory ossicles. The final chapter presents a historical survey of the structure and function of the internal ear, covering the period from 550 B.C. to the present. Bibliographies are appended to the various chapters. There are good indexes of authors and subjects. The book is well published, and the illustrations are excellent. Considering the large number of expensive figures and plates, the price of the book is not excessive. The volume should be in all medical libraries and in the libraries of otologists and anatomists.

Nutrition and Diet in Health and Disease. By James S. McLester, M.D., professor of medicine, University of Alabama School of Medicine. Fifth edition. 8°, cloth, 800 pp. Philadelphia: W. B. Saunders Company, 1949. $9.00.

This standard treatise was first published in 1927, and the last edition was printed in 1943. In this new edition much of the text has been rewritten, and the work now conforms to the knowledge gained during the war years. A section on folic acid has been added, and the material on the vitamins and their functions, on deficiency diseases and on protein has been revised. The more liberal diet now used in peptic ulcer and the high-protein regimens used in cirrhosis and other diseases of the liver are discussed; data on the low-salt diet for congestive heart failure and the sodium-free diet for arterial hypertension have been added. New food tables have been included in the text. The chapters on the feeding of infants, by Dr. Philip Jeans, and on nutrition in industry, by Dr. Robert S. Goodhart, have been entirely rewritten. There is a new chapter on the feeding of surgical patients by Dr. Charles C. Lund, of Boston. There is a comprehensive index, and the book is well published in every way. The use of a lightweight paper has resulted in a book light in weight for its size. The volume should be in all medical libraries and should prove valuable to the practicing physician as a standard reference text.

A Primer of Electrocardiography. By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, senior visiting physician, Charity Hospital, consultant in cardiovascular diseases, Ochsner Clinic, and visiting physician, Touro Infirmary, New Orleans; and Travis Winsor, M.D., assistant clinical professor of medicine, University of Southern California School of Medicine, director of Nash Cardiovascular Foundation, Hospital of the Good Samaritan, junior attending physician, Los Angeles County Hospital, and junior attending physician, Children's Hospital, Cardiac Department, Los Angeles. Second edition. 8°, cloth, 245 pp., with 265 illustrations. Philadelphia: Lea and Febiger, 1949. $4.50.

This primer, intended for the beginner, has been revised in certain particulars. The bipolar precordial leads have been replaced by the unipolar leads, and it is recommended that they be employed exclusively with the standard leads in clinical electrocardiography. The book is well published, and the illustrations are excellent.

Poliomyelitis: Papers and discussions presented at the First International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. 4°, cloth, 360 pp. with 92 illustrations and 52 tables. Philadelphia: J. B. Lippincott Company, 1949. $5.00.

This volume constitutes the transactions of the first world conference on poliomyelitis. There were ten sessions, and the papers read covered the whole field of the subject. The volume is essential to all medical libraries. The book is well published.

Diseases of Children. Volume II. Edited by Donald Paterson, M.D. (Edin.), F.R.C.P., consulting physician, Hospital for Sick Children, Great Ormond Street, and consulting physician in charge of diseases of children, Westminster Hospital; and Alan Moncrieff, M.D. (Lond.), F.R.C.P., Nuffield Professor of Child Health, University of London, physician, Hospital for Sick Children, Great Ormond Street, and consulting physician, Children's Department, Middlesex Hospital. Fourth edition. 8°, cloth, 1033 pp., with 380 illustrations. Baltimore: Williams and Wilkins Company, 1949. $10.00.

This second volume of a well known British treatise on pediatrics is the joint work of twenty-four contributors, specialists in their particular fields. The material covered in this volume comprises diseases of the nervous system, congenital mental defect in childhood, diseases of the eyes, diseases of the muscles, bones and joints, orthopedic surgery, diseases of the genitourinary and digestive systems and the peritoneum, rheumatism, diseases of the cardiovascular system and of the blood, infectious diseases, venereal disease and diseases of the skin, and malignant lesions in childhood. There is a good index. The text was printed in Great Britain. The treatise should be in all pediatric collections in medical libraries.

Doctors of Infamy: The story of the Nazi medical crimes. By Alexander Mitscherlich, M.D., head of the German medical commission to Military Tribunal No. 1, Nuremberg; and Fred Mielke. Translated by Heinz Norden. With statements by three American authorities identified with the Nuremberg medical trial: Andrew C. Ivy, M.D., vice-president, University of Illinois, and medical scientific consultant to the prosecution, Military Tribunal No. 1, Nuremberg; Telford Taylor, brigadier general, United States Army, Chief of Counsel for War Crimes; and Leo Alexander, M.D., psychiatrist, consultant to the Secretary of War and to the Chief of Counsel for War Crimes; and a note on medical ethics by Albert Deutsch (including the new hippocratic oath of the World Medical Association). 8°, cloth, 172 pp., with 16 pages of photographs. New York: Henry Schuman, 1949. $3.00.

This book is mainly a translation of *Das Diktat der Menschenverachtung*, published by the two principal authors at Heidelberg in 1947. It constitutes the story of the famous Nuremberg medical trial of 1946–1947, before Military Tribunal No. 1. The two German authors attended the trial as delegates chosen by a group of German medical societies and universities. They were treated with the utmost courtesy and accorded the same privileges as the working press, with free access to all documents and testimony. They have rendered in the main part of this book a fair and impartial report on the proceedings of the trial. The defendants comprised 20 physicians of high rank in the German organization and 3 high-ranking civilian aids, 2 of whom were formerly attached to Hitler and Himmler. The text concerns the medical experimentation carried on at various concentration camps, the collection of skulls of Jews and the euthanasia program. Seven of the defendants were acquitted and freed, 7 were sentenced to death, and 9 received prison sentences of varying lengths.

The Uses of Penicillin and Streptomycin. By Chester S. Keefer, M.D., Wade Professor of Medicine, Boston University School of Medicine, and director of Evans Memorial and physician-in-chief of the Massachusetts Memorial Hospitals. 8°, cloth, 72 pp. Lawrence, Kansas: University of Kansas Press, 1949. $2.00. Porter Lectures, Series 15.

In this small volume are gathered the three Porter lectures given by Dr. Keefer under the auspices of the University of Kansas School of Medicine. They present a summary of the latest knowledge on two important therapeutic agents. The first lecture is entitled "Penicillin in Medical and Surgical Practice," the second "Streptomycin in the Treatment of Infections," and the third "Antibacterial Agents from Microbes." The last lecture comprises a short history of the subject. Dr. Keefer is recognized as an outstanding authority on penicillin and similar agents. Rather surprisingly, there is a good index to the small volume. The book is well published and should be in all medical libraries.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A Tuesday evening lecture sponsored by the Boston City Hospital House Officers' Association will be presented in the Dowling Amphitheater, Boston City Hospital, on December 13 at 7 p.m. Dr. Harry Eagle will speak on the subject "The Factors of Time and Dosage in the Therapeutic Use of Penicillin." The discussion will be led by Drs. Maxwell Finland and Chester S. Keefer.

All interested physicians are invited to attend.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, December 20, at 12 noon. Dr. Duncan E. Reid will speak on the subject "Experiences with a Recent Medical Mission to Germany."

Physicians are cordially invited to attend.

BOSTON LYING-IN HOSPITAL OBSTETRIC ROUND TABLE

The following schedule of obstetric round-table conferences for visiting physicians will be held at the Boston Lying-in Hospital at 7 p.m. on the dates indicated:

December 19, 1949. Early Trimester Bleeding (Clinical, Pathological and Hormonal Aspects). Drs. H. Bristol Nelson, Arthur T. Hertig and George Van S. and Olive W. Smith.

February 20, 1950. Toxemia of Pregnancy (Obstetric Management and Treatment of the Complications of Oliguria and Anuria). Drs. Duncan Reid and John Merrill.

April 17, 1950. Problems of Labor in the Potentially Infected Patient (Tests of Labor, Methods of Delivery and Chemotherapy). Drs. Samuel B. Kirkwood, M. Fletcher Eades and Maxwell Finland.

Visiting physicians are invited to avail themselves of the Boston Lying-in Hospital cafeteria until 6 p.m.

INTERNATIONAL SOCIETY OF HEMATOLOGY

The Biennial Congress of the International Society of Hematology will be held at the University of Cambridge, Cambridge, England, August 21 through 26, 1950.

The program committee is in the process of receiving titles for papers and scientific exhibits to be presented at the Congress. Material to be submitted for consideration for the program may be sent to Dr. I. Davidsohn, Mt. Sinai Hospital, Chicago, Illinois, or Dr. S. Mettier, University of California, San Francisco, California. Those desiring to present scientific exhibits should make application as soon as possible.

COURSES IN RADIOISOTOPE TECHNICS

Some vacancies still remain for the winter series of three courses in radioisotope technics offered by the Special Training Division of the Oak Ridge Institute of Nuclear Studies. Interested persons who can attend a course during the winter months are urged to make application for one of these courses in view of the heavy load of applications from university people for participation in the summer courses. The courses will begin on January 2, January 30 and March 6, 1950. Applications should be made as soon as possible. Eleven of the courses have already been given. Thirty-two participants can be accommodated in each of the three four-week courses. Requests for application and additional information should be addressed to Dr. Ralph T. Overman, chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

(*Notices concluded on page xi*)